Filed by: Sally Gardner Lane
Administrative Patent Judge
Box Interference
Washington, D.C. 20231
Tel: 703-308-9797
Fax: 703-305-0942

Paper 1

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

JEANNE **DIETZ-BAND**,
WANG-TING HSIEH, and JOHN F. CONNAUGTON

Junior Party,
(Patent 6,414,133),

v.

JOE W. **GRAY**,
DANIEL PINKEL, and DOUGLAS TKACHUK

Senior Party,
(Application 10/608,092).

Patent Interference No. 105,208

DECLARATION

Part A. Declaration of interference

An interference is declared (35 U.S.C. § 135(a)) between the above-identified parties.

Details of the patent, application, count, and claims designated as corresponding or as not corresponding to the counts appear in Parts E and F of this NOTICE DECLARING INTERFERENCE.

Part B. Judge designated to handle the interference

Administrative Patent Judge Sally Gardner Lane has been designated to handle the interference. 37 CFR § 1.610(a).

Part C. Standing order

A Trial Section STANDING ORDER accompanies this NOTICE DECLARING INTERFERENCE. The STANDING ORDER applies to this interference.

The Board is conducting a DVD pilot project. A copy of the procedure is attached to this order.

Part D. Conference call to set dates

A telephone conference call to set dates for taking action in the interference is scheduled for **2:30 p.m. on 8 June 2004** (the call will be initiated from the PTO).

No later than **two business days** prior to the conference call, each party shall file and serve by facsimile a list of the preliminary motions the party intends to file. See § 17 of the STANDING ORDER.

A copy of a "sample" order setting times for taking action during the preliminary motion phase of the interference accompanies this NOTICE DECLARING INTERFERENCE.

Counsel are encouraged to discuss the order prior to the conference call with the view to coming to some mutual agreement as to dates for taking action. A typical preliminary motion period lasts approximately nine (9) months. Counsel should be prepared to justify any request for a shorter or longer period.

The Board is conducting an electronic filing pilot project. A copy of the procedure is attached to this order. Counsel should be prepared to discuss participation in the pilot project.

Part E. The parties involved in this interference are:

	Junior Party
Named inventors:	JEANNE DIETZ-BAND Deerwood, Maryland WANG-TING-HSIEH Bethesda, Maryland JOHN F. CONNAUGTON Laytonsville, Maryland
Application:	09/170,630, filed 13 October 1998, issued as patent 6,414,133 on 2 July 2002
Title:	MULTIPLE FUSION PROBES
Assignee:	Ventana Medical Systems, Inc.
Accorded Benefit:	None
Attorneys:	See last page
Address:	See last page

Senior Party

Named Inventors:	JOE W. GRAY Livermore, CA DANIEL PINKEL Walnut Creek, CA DOUGLAS TKACHUK Livermore, CA
Application:	10/608,092 filed 30 June 2003 (IFW IMAGE)
Title:	CHROMOSOME-SPECIFIC STAINING TO DETECT GENETIC REARRANGEMENTS
Assignee:	None of record
Accorded Benefit:	US 09/765,291, filed 22 January 2001 (IFW IMAGE); US 08/487,974, filed 7 June 1995, issued as patent 6,280,929 on 28 August 2001; US 08/342,028, filed 16 November 1994; US 08/181,367, filed 14 January 1994; US 08/054,353, filed 28 April 1993; and US 07/537,305, filed 12 June 1990
Attorneys:	See last page
Address:	See last page

Part F. Count and claims of the parties

Count 1

Claim 1 or claim 10 of Dietz-Band (6,414,133) or claim 127 of Gray (10/608,092).

The claims of the parties are:

Dietz-Band: 1-19

Gray: 127-143

The claims of the parties which correspond to Count 1 are:

Dietz-Band: 1-3, 5-12, and 14-19

Gray: 127-143

The claims of the parties which do not correspond to Count 1 are:

Dietz-Band: 4 and 13

Gray: None

Part G. Heading be used on papers

The following heading shall be used on papers filed in the interference. See § 18 of the STANDING ORDER.

Paper ___

Filed on behalf of [name of party]
By: Name of lead counsel, Esq.
Name of backup counsel, Esq.
Street address
City, State, and Zip-Code
Tel:
Fax:

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES
(Administrative Patent Judge Sally Gardner Lane)

JEANNE **DIETZ-BAND**,
WANG-TING HSIEH, and JOHN F. CONNAUGTON

Junior Party,
(Patent 6,414,133),

v.

JOE W. **GRAY**,
DANIEL PINKEL, and DOUGLAS TKACHUK

Senior Party,
(Application 10/608,092).

Patent Interference No. 105,208

TITLE OF PAPER

Part H. Summary of dates for taking action

Times for taking action are set out in the following sections of the STANDING ORDER:

1. § 7: date for identifying lead and backup counsel.

2. § 8: date for identifying any real party in interest.

3. § 9: date for requesting copies of involved and benefit applications and patents.

4. § 17: date for filing list of proposed preliminary motions.

5. § 19: date for accomplishing certain discovery.

6. § 20: date for filing clean copy of claims.

7. § 21: date for filing clean copy of claims in cases with drawings and/or claims containing a means plus function limitation.

8. § 23: dates for filing oppositions to Rule 635 miscellaneous motions and dates for filing replies to oppositions.

9. § 33: date for objecting to admissibility of evidence.

10. § 34: date for serving supplemental affidavits or evidence to respond to objection to admissibility of evidence.

11. § 35: dates when cross-examination can take place.

12. § 45: dates for taking action with respect to settlement discussions

Part I: Order form for requesting file copies

FILE COPY REQUEST

Interference 105,208

A copy of Part E of this NOTICE DECLARING INTERFERENCE should be attached to this FILE COPY REQUEST, with a circle by hand around the patents and applications for which a copy of a file wrapper is desired.

To facilitate processing of this FILE COPY REQUEST, the following information should be included:

1. Charge fees to USPTO Deposit Account No. _____

2. Complete address, including street, city, state, zip code and telephone number (do not list a Post Office box inasmuch as file copies are sent via commercial overnight courier).

_____

_____

_____

_____

Telephone, including area code: _____

Part J. Signature of administrative patent judge

SALLY GARDNER LANE
Administrative Patent Judge

29 March 2004
Arlington, VA

Enc:

Copy of STANDING ORDER

Copy of order used for setting times for taking action in the preliminary motion phase of the interference (ORDERPM6)

Copy of order used for setting times for taking action in the testimony and briefing phases of the interference (ORDERTE6)

PTO Form 850

Copy of pending claims in 10/608,092

Copy of US 6,414,133

Copy of electronic filing order

Copy of DVD evidence order

DECLARE.007
Revised 12 October 2000
(replaces DECLARE.006.1)

cc (via overnight carrier):

Attorney for Dietz-Band (real party in interest:Ventana Medical Systems, Inc.):

Huw R. Jones, Esq.
VENTANA MEDICAL SYSTEMS, INC.
1910 Innovation Park Drive
Tucson, AZ 85737

Attorney for Gray:

BURNS, DOANE, SWECKER & MATHIS LLP
1737 King Street, Suite 500
Alexandria, VA 22314

UNITED STATES PATENT AND TRADEMARK OFFICE

BOARD OF PATENT APPEALS AND INTERFERENCES
INTERFERENCE DIVISION
Trial Section

STANDING ORDER
(Governing proceedings before the Trial Section)

1 May 2003

1 Communications with the Board

1.1 No *ex parte* communications

Communications with an administrative patent judge relating to an interference shall be *inter partes* in which at least one counsel for each party shall participate. Any attempt to initiate an *ex parte* telephone call, e-mail, or other form of communication to an administrative patent judge in connection with an interference may result in sanctions.

1.2 Telephone calls to the board

Telephone calls to the board regarding an interference shall be placed to 703-308-9797.

Telephone calls requesting a conference call shall be placed to personnel of the support staff assigned to the Trial Section of the Interference Division of the board. A party seeking a conference call with an administrative patent judge should be prepared to advise the support staff personnel why a conference call is needed.

1.3 Filing papers with the board

1.3.1 Certificates of service

Proof of service must accompany all papers filed in an interference. 37 CFR § 1.646(e).

Each paper filed in an interference shall have a separate certificate of service, which shall be the last page of the paper. The purpose for this requirement is to make it easier for the board to verify that each paper in an interference has been served.

The certificate of service serves as notice to an opponent that the paper has been filed with the board.

1.3.2 Transmittal sheets

The filing of a transmittal sheet listing documents being filed unduly complicates entry of papers into files and docketing of papers in the Office of the Clerk. The filing of papers in the nature of a transmittal sheet is not authorized.

1.3.3 Delivery of papers to the board

Papers may be delivered to the board as follows:

1.3.3.1 Hand delivery to the board

Hand-delivery to the board must occur between the hours of 8:30 a.m. and 5:00 p.m. The board is located at:

Board of Patent Appeals and Interferences
Crystal Gateway Two
10th Floor
1225 Jefferson Davis Highway
Arlington, Virginia 22202

Any paper hand-delivered to the Office of the Clerk before 10:00 a.m. is deemed to have been filed the previous business day provided the paper was properly served the previous business day. The ability to file a paper with the board by 10:00 a.m. is designed to eliminate any need to hand-deliver papers to the United States Patent and Trademark Office (USPTO) Mail Room after business hours.

Hand-delivery to the Office of the Clerk of the Board will minimize the time it takes to (1) process the paper and (2) decide any request made in the paper.

1.3.3.2 Commercial overnight delivery service

Commercial overnight delivery service, addressed as follows:

Board of Patent Appeals and Interferences

Crystal Gateway Two, 10th Floor

1225 Jefferson Davis Highway

Arlington, VA 22202

Properly addressed papers filed by a commercial overnight delivery service are deemed filed on the date they are delivered to the commercial overnight delivery service.

1.3.3.3 United States Postal Service

Delivery to the USPTO Mail Room or by U.S. Postal Service, including EXPRESS MAIL®, addressed as follows:

Mail Stop INTERFERENCE

Board of Patent Appeals and Interferences

United States Patent and Trademark Office

Alexandria, Virginia 22313-1450.

1.3.3.4 Facsimile

The board facsimile number for interference matters is 703-305-0942.

Papers exceeding five (5) pages in length cannot be filed by facsimile without prior permission of Trial Section support staff personnel.

Unless expressly ordered by an administrative patent judge, a subsequent confirmation copy is not needed when filing a paper by facsimile.

2 Service

2.1 Service of papers by hand or EXPRESS MAIL®

All papers served on opposing counsel in an interference shall be served by:

(a) EXPRESS MAIL® (an overnight delivery service of the U.S. Postal Service) (37 CFR § 1.646(d)) or

(b) any other means that accomplishes a same-day or overnight delivery of the paper, e.g., by hand, facsimile, or a commercial overnight delivery service.

The purpose of this requirement is to place all parties on a level playing field by avoiding different delivery times, which inherently occur through the use of the U.S. Postal Service.

Unless agreed to by the parties, electronic mail is not deemed to be service.

The day a facsimile is transmitted, an overnight package is delivered to a courier or a paper is served by hand does not count in the calculating of the time for filing a response.

2.2 Papers served that need not be filed

The following papers, which must be served on an opponent, need not be filed with the board at the time of service, but may need to be filed at a future date if a dispute arises with respect to the paper served:

(a) An objection to the admissibility of evidence after service of evidence (the objection should be filed only as an attachment to a motion to exclude (37 CFR § 1.656(h)).

(b) A notice requesting cross-examination.

(c) Discovery pursuant to ¶ 7(a) of this STANDING ORDER.

3 Paper format

3.1 Cover sheet to be used in filing papers

The first page of all papers filed in an interference shall be **pink** similar to the pink first sheet accompanying the NOTICE DECLARING INTERFERENCE.

3.2 Requirement for filing two copies of each paper

Unless otherwise ordered, a party is required to submit (1) an original and (2) one copy of each paper filed in an interference. The copy shall be marked at the top:

"COPY FOR JUDGE"

3.3 **Size of paper**

With the exception of original exhibits of a different size, all papers filed in an interference shall be:

(a) 8½ inch x 11 inch paper or

(b) A4 paper.

The board prefers use of 8½ inch x 11 inch paper. The purpose of this requirement is to facilitate storage of papers, files and evidence at the board and placing of papers in file wrappers.

3.4 **Holes at the top of papers**

All papers filed in an interference shall have two holes punched at the top spaced at 2-3/4 inches apart (each hole spaced equidistant from an imaginary center line running from the top to the bottom of the paper).

The purpose of this requirement is to facilitate placing papers in files and to avoid the need to unstaple papers, thereby minimizing the chance that a page of a particular paper will be inadvertently separated or misplaced.

3.5 **Headings on papers**

In papers filed in an interference, the heading shown in Part G of the NOTICE DECLARING INTERFERENCE shall be used. Standardized headings have proved to be important in improving the processing of papers at the board and facilitate communications with the parties.

3.6 **Manner of styling papers**

The style of all papers shall appear on a single line and shall not use the words "et al".

The purpose of this requirement is to simplify docketing at the board.

All motions, including 37 CFR § 1.633 preliminary motions, of a party shall be consecutively numbered starting with number 1. In connection with a motion, and in a second line, a party may specify the nature of the motion. For example:

(a) JONES MISCELLANEOUS MOTION 1
(for additional discovery)

(b) JONES PRELIMINARY MOTION 2
(for judgment based on prior art)

(c) JONES PRELIMINARY MOTION 3
(for judgment based on lack of enablement)

(d) JONES MOTION TO CORRECT INVENTORSHIP 4

Any opposition to a motion, including a 37 CFR § 1.633 preliminary motion, shall bear the same number as the motion it opposes (skipping the number of any motion not opposed). For example:

(e) SMITH OPPOSITION 1

(f) SMITH OPPOSITION 2

(g) SMITH OPPOSITION 4

Any reply to an opposition shall bear the same number as the opposition to which it replies (again, skipping the number of any opposition for which no reply is filed). For example:

(h) JONES REPLY 1

(i) JONES REPLY 4

Papers other than motions, oppositions and replies should be similarly styled. For example:

(j) JONES DESIGNATION OF LEAD ATTORNEY

(k) SMITH DESIGNATION OF REAL PARTY IN INTEREST

(l) JONES REQUEST FOR FILE COPIES

(m) SMITH PRELIMINARY STATEMENT

(n) JONES SERVICE OF REFERENCES

(o) SMITH CLEAN COPY OF CLAIMS

(p) SMITH CLEAN COPY OF CLAIMS
(with drawing numerals)

(q) SMITH CLEAN COPY OF CLAIMS
(means plus function)

3.7 Use of double spacing

All typing in papers (including quotes and footnotes, but excluding headings, signature blocks and certificates of service) shall be double spaced.

The use of footnotes is discouraged.

3.8 Prohibition against presenting duplicate papers

When presenting a paper in an interference, a party shall not submit with the paper (as an appendix, exhibit, or otherwise) a copy of a paper previously filed in the interference (37 CFR § 1.618(b)).

The purpose of this requirement is to (1) minimize the size of files and (2) facilitate storage of material in the limited storage space available to the board.

4 Lead and backup counsel

Within **fourteen (14)** days of the date of the NOTICE DECLARING INTERFERENCE, each party is required to identify in a separate paper:

(a) a lead counsel (37 CFR § 1.613(a));

(b) a backup lead counsel;

(c) a mailing address;

(d) in the event the mailing address is a Post Office Box, an additional address where overnight packages may be delivered (a commercial courier will not deliver to a U.S. Postal Service box);

(e) telephone number;

(f) facsimile number and

(g) internet e-mail address, if available.

If lead counsel or backup counsel are not counsel of record (37 CFR § 1.34(b)) in the application or patent involved in the interference, then within **fourteen (14) days** of the date of the NOTICE DECLARING INTERFERENCE, a power of attorney shall be filed.

5 **Real party in interest**

Within **fourteen (14) days** of the date of the NOTICE DECLARING INTERFERENCE, each party shall notify the board in a separate paper of any and all right, title, and interest in any application or patent involved in the interference (37 CFR § 1.602(b)).

All parties are continually obligated to promptly update changes of the real party in interest.

6 **Request for file copies**

The parties to the interference have access to the patent and application files involved in the interference, as well as any benefit files identified in the NOTICE DECLARING INTERFERENCE. 37 CFR § 1.612(a).

The parties are advised that the interference file does not include any involved application or patent or any benefit files, all of which are maintained separate from the interference file. If a party wishes to order copies of involved application or patent files or any benefit files mentioned in the NOTICE DECLARING INTERFERENCE, then within **fourteen (14) days** of the date of the NOTICE DECLARING INTERFERENCE, the party shall file **with the board** (not another office in the USPTO) a separate paper styled [Name of party] REQUEST FOR FILE COPIES to which is attached a completed FILE COPY REQUEST, a copy of which accompanies the NOTICE DECLARING INTERFERENCE.

The parties are encouraged to file requests for copies by facsimile at 703-305-0942.

Within **twenty-one (21) days** of the date of the NOTICE DECLARING INTERFERENCE, the board will forward all requests timely received and all necessary files to the Office of Public Records (OPR).

An order will be entered by the Trial Section notifying the parties that their respective orders have been forwarded to OPR. OPR will make the copies, which will be shipped via overnight commercial courier within **fourteen (14) days** of receipt of the order.

The parties are advised that during the pendency of the interference, files may be inspected only at the board and generally are unavailable while copies are being made at OPR.

The parties are further advised that failure to timely request copies of files as set out herein generally will not constitute a basis for granting an extension of time (37 CFR § 1.645(a)). Thus, an extension of time should not be expected based on non-receipt of requested files where a party did not timely place an order for copies in the manner set out above.

7 **Copies of patents and literature mentioned in each specification (and translations, if available)**

Within **twenty-one (21) days** of a request by an opponent, a party shall:

(a) serve a legible copy of every requested patent, literature reference, and test standard (e.g., an ASTM test) mentioned in the specification of the party's involved patent or application upon which the party will rely for benefit;

(b) in the case of any patent, literature reference, or test standard in a foreign language, serve any translation to which the party has access; and

(c) file with the board a notice (without copies of the patents or literature) that it has served the patents and literature.

Upon a request by the board, the parties should be prepared to promptly file copies of the patent, literature references, or test standards.

The purpose of the additional discovery authorized by this section is (1) to place the parties on a level playing field and (2) to minimize any difficulty authenticating documents when a party would like to rely on a document cited in an opponent's specification. A party should have access to documents cited in its opponent's specification and it may be difficult for the party to locate those documents. 37 CFR § 1.687(c).

8 **Clean copy of claims**

Within **fourteen (14) days** of the date of the NOTICE DECLARING INTERFERENCE, each party shall file a copy of a clean set of all claims (as they exist as of the date of the NOTICE DECLARING INTERFERENCE):

(a) pending in the party's involved application or

(b) contained in the party's involved patent (including any changes that took place by way of a certificate of correction after granting of the patent and before the NOTICE DECLARING INTERFERENCE).

In a biotechnology case, if the claims refer to a sequence, then a copy of the sequence shall be included along with the clean copy of the claims.

The purpose of this requirement is to have readily available a clean copy of the claims of the parties. In applications, claims are often spread throughout the application file. In patents, there are often certificates of correction.

9 **Application or patent with a drawing or claims containing means or step for performing a specified function limitations**

If any involved patent or application contains:

(1) a drawing or

(2) a claim designated as corresponding to a count reciting a means or step for performing a specified function (35 U.S.C. 112[6]),

then within **twenty-eight (28) days** of the date of the NOTICE DECLARING INTERFERENCE, the party is required to file (in addition to the paper required by ¶ 8 of this STANDING ORDER) a separate paper containing a copy of the claims in which:

(a) following each element recited in each claim, the drawing numbers corresponding to that element are inserted in bold in braces, e.g., { } and

(b) following each means or step for performing a specified function are inserted in bold in braces { }, all structure, material or acts described in the specification corresponding to that means or step (by citation to the page(s) and line(s) of the specification or figure and item number of the drawings).

An example follows:

An apparatus comprising

a pump { **Fig. 1, item 18** },

a body member { **Fig. 1, item 19** },

a first valve { **Fig. 2, item 25** },

means for calculating a numerical value for an exponent { **page 2, lines 8-10; page 4, lines 21-25; Fig. 2, item 34** },

means for printing { **page 5, line 8 through page 6, line 1; Fig. 3, items 45 and 46** }, and

a second valve { **Fig. 3, item 98** } * * *.

The purpose of this requirement is to allow all parties and the board to understand the precise scope of the claims that correspond to the count. Since a count may itself refer to a party's claim that contains a means or step for performing a specified function, the requirement will also make it easier to understand the scope of a count.

If during an interference, a party presents (1) a new claim in an application that contains a drawing or (2) a new claim that recites a means or step for performing a specified function, the party shall file a separate paper containing a copy of the new or amended claim complying with the requirements set out above.

If during an interference, a party files a 37 CFR § 1.633 preliminary motion seeking the benefit of an earlier application (1) containing a drawing or (2) with respect to a claim in an involved patent or application that recites a means or step for performing a specified function, the

party shall file an appendix to the 37 CFR § 1.633 preliminary motion containing a copy of the claims complying with the requirements set out above.

If during an interference, a party intends to argue that a structure, material or act is an equivalent (within the meaning of 35 U.S.C. 112[6]) of a structure, material or act described in the specification, then the party shall:

(a) promptly file a notice with the board of its intention to argue the equivalency;

(b) clearly set out the precise nature of the structure, material or act that is deemed to be equivalent to the structure, material or act described in the specification and

(c) bear the burden of proof of establishing the equivalency alleged.

In the case of a 37 CFR § 1.633 preliminary motion, notice is deemed to be promptly given if it is given in the 37 CFR § 1.633 preliminary motion or, if raised by an opponent, in an opposition to a 37 CFR § 1.633 preliminary motion.

In the case of priority, notice is deemed to be promptly given if a separate paper is filed with the board at the same time a party serves its case-in-chief. See § C, ¶¶ 2 and 5 of the ORDER SETTING TIMES (Times for taking action--priority testimony phase).

Conference calls to set dates

Dates for action in an interference are generally, but not always, set after a conference call.

In the case of dates for taking action during the preliminary motion and priority testimony phase of the interference, the call generally will be initiated by the board.

A date and time for a conference call to discuss dates for taking action during the preliminary motion phase of the interference has been set in Part D of the NOTICE DECLARING INTERFERENCE.

No later than **two business days** prior to the conference call to set dates for taking action during the preliminary motion phase, each party shall file and serve by facsimile a list of the 37 CFR § 1.633 preliminary motions the party intends to file.

The requirement for a list of 37 CFR § 1.633 preliminary motions attempts to improve the administration of justice, including reducing costs, by (1) helping the Trial Section and counsel arrive at an appropriate schedule for taking action during the preliminary motion phase of the interference, (2) permitting the Trial Section to determine that certain 37 CFR § 1.633 preliminary motions may be unnecessary and that other 37 CFR § 1.633 preliminary motions may be necessary and (3) revealing the possibility that there may be a dispositive 37 CFR § 1.633 preliminary motion. Submission of a list does not preclude the filing of additional 37 CFR § 1.633 preliminary motions not contained in the list. However, subsequent determination of a need to file an additional 37 CFR § 1.633 preliminary motion will not constitute a basis for enlarging the time for taking action in the preliminary motion phase.

A copy of a "sample" order setting times for taking action during the preliminary motion phase of the interference accompanies the NOTICE DECLARING INTERFERENCE. Counsel are encouraged to discuss the order prior to the conference call and to come to some mutual agreement as to dates for taking action.

11 Legal authorities

11.1 Citation of precedent and other authority

When citing a decision of a court that is published in both the West Reporter System and the United States Patents Quarterly (USPQ), counsel should provide parallel citations, e.g., Aelony v. Arni, 547 F.2d 566, 192 USPQ 486 (CCPA 1977); In re Deckler, 977 F.2d 1449, 24 USPQ2d 1448 (Fed. Cir. 1992).

Binding precedent is the following:

(a) Decisions of the U.S. Supreme Court.

(b) Decisions of the Court of Appeals for the Federal Circuit, the former CCPA and the former Court of Claims. See South Corp. v. United States, 690 F.2d 1368, 1370-71, 215 USPQ 657, 657-58 (Fed. Cir. 1982) (en banc), and In re Gosteli, 872 F.2d 1008, 1011, 10 USPQ2d 1614, 1616-17 (Fed. Cir. 1989) (where there is

a conflict between two or more decisions of the former CCPA, the later CCPA decision controls).

(c) Decisions of the Director of the USPTO (formerly the Commissioner of Patents and Trademarks).

(d) Decisions of the Board of Patent Appeals and Interferences that have been determined to be binding precedent in accordance with board Standard Operating Procedure 2. See, e.g., Reitz v. Inoue, 39 USPQ2d 1838 (Bd. Pat. App. & Int. 1995).

(e) Trial Section decisions that have been designated as precedential.

Decisions of the regional courts of appeals and the district courts may be cited, but are not binding precedent.

Non-precedential decisions of federal courts shall not be cited.

Non-precedential decisions of the board may be cited, but are not binding.

The Manual of Patent Examining Procedure (MPEP) is a guide for patent examiners, which is prepared by the Office of the Commissioner for Patents. Counsel should cite only primary authority: (1) the United States Code, (2) the Code of Federal Regulations, (3) notices published in the Federal Register or the Official Gazette, and (4) binding precedent.

11.2 Copies of authority cited

Parties are required to submit with the document in which a court opinion is cited a copy of any opinion that is **not** reported in (1) West Publishing Company's Supreme Court Reporter, (2) the second or third series of West's Federal Reports, or (3) the first or second series of the USPQ. The reason for this requirement is that other court reporters are not available at the board.

11.3 Trial Section opinions

Trial Section binding precedents and other selected Trial Section opinions are available through the internet at:

http://www.uspto.gov/web/offices/dcom/bpai/its.htm

The web page is updated from time to time.

Opinions may also be published in the USPQ2d.

12 Copy of papers in electronic form

The purpose of this section is to put the parties on notice that they are authorized to file copies of documents in electronic form. Often documents in electronic form (1) are more easily searched and (2) can minimize the chance that an argument or evidence will be overlooked by an administrative patent judge or other board personnel.

The required number of paper copies must also be filed in the USPTO and served on all opponents.

12.1 Time and medium for electronic filing

At an appropriate time in the proceeding, the board will authorize submission of (1) a 100mb ZIP® disk for a ZIP® disk drive or (2) a CD-ROM.

12.2 Papers appropriate for electronic filing

The following documents are appropriate for submission on the ZIP® disk or CD-ROM:

(a) the specification,

(b) the claims,

(c) any motion, opposition or reply,

(d) affidavit testimony,

(e) exhibits,

(f) transcripts of cross-examination depositions,

(g) principal, opposition and reply briefs at final hearing and

(h) other material, such as statutes, rules and court and administrative precedent relied upon in 37 CFR § 1.633 preliminary motions, principal briefs, oppositions or replies.

12.3 Format

The filing of a ZIP® disk or CD-ROM is subject to the following conditions:

(a) The ZIP® disk or CD-ROM must be capable of operating on a computer running Windows NT.

(b) The board has monitor capability of 256 colors and an 800 x 600 screen setting.

(c) The board will not consider electronic files submitted in formats it cannot read. The board has access to ADOBE ACROBAT READER (preferably in the text-searchable format), WORDPERFECT 9, and MICROSOFT WORD 2000. Parties use other formats at their own risk.

(d) The file name of each electronic document must concisely identify the content of the document (e.g., Jones PM1.wpd, Smith Opp1.doc; Ex1038.pdf).

(e) Any party wishing to file the brief on ZIP® disk or CD-ROM must provide four (4) copies of the ZIP® disk or CD-ROM to the board.

(f) One copy of the ZIP® disk or CD-ROM must be served on all opponents.

13 Motions, oppositions and replies

The purposes of the following requirements are to (1) simplify consideration of motions, (2) minimize the chance that an argument will be overlooked and (3) make it easier to determine whether a reply raises new issues.

13.1 Motions

13.1.1 Burden of proof

A party filing a motion has the burden of proof. 37 CFR § 1.637(a). In addition to complying with any procedural requirements of the rules and this STANDING ORDER, when a substantive issue is raised by a motion, a party bears a burden to establish its right to any substantive relief requested in the motion. See Hillman v. Shyamala, 55 USPQ2d 1220, 1221-22 (Bd. Pat. App. & Int. 2000). A motion that fails to comply with applicable procedural requirements may be dismissed without reaching the merits, in which case the issue sought to be raised by the motion is deemed not to have been properly presented for decision by the board. A motion that, while complying with applicable procedural requirements, nevertheless fails to make

out a substantive case may be denied on the merits. A motion may be dismissed or denied without considering the opposition and may be granted without considering the reply.

13.1.2 Format

In presenting a motion, a party shall set out in the following order:

(a) The precise relief requested. Two examples are:

(1) Jones moves to be accorded the benefit of the filing date of application X, filed January 22, 1993.

(2) Jones moves for judgment against Smith on the ground that Smith's claims 1, 2 and 5 corresponding to the count are unpatentable under 35 U.S.C. 103 over the combined disclosures of U.S. Patent No. Y (Johnson) and French Patent Z (Boleau).

(b) The evidence (i.e., a list in numerical order of all exhibits) upon which the moving party relies in support of the motion with a brief description of the exhibit (e.g., "Exhibit 1038, Second Declaration of Jones").

(c) A statement of facts in separately numbered paragraphs sufficient to establish entitlement to the requested relief, with citations to the evidence.

(d) An argument setting out the reasons why relief should be granted.

Facts should be set out as short, numbered declaratory sentences that are capable of being admitted or denied.

A motion may be denied if the facts alleged are insufficient to state a claim for which relief may be granted. Facts set out in an argument portion of a motion may be overlooked and may result in a motion being denied.

Citation to the evidence must be specific, i.e., (1) by column and line of a patent, (2) page, column and paragraph of a journal article and (3) page and line of a cross-examination deposition transcript. Citations to an entire document or numerous pages of a cross-examination deposition transcript do not comply with the requirement for a citation to the record. In this

respect, the Trial Section adopts as its policy the rationale of Clintec Nutrition Co. v. Baxa Corp., 44 USPQ2d 1719, 1723 n.16 (N.D. Ill. 1997), which notes that where a party points the court to multi-page exhibits without citing a specific portion or page, the court will not pore over the documents to extract the relevant information, citing United States v. Dunkel, 927 F.2d 955, 956 (7th Cir. 1991). Nor will the board take on the role of an advocate for one of the parties. Cf. Ernst Haas Studio, Inc. v. Palm Press, Inc., 164 F.3d 110, 111-12, 49 USPQ2d 1377, 1378-79 (2d Cir. 1999).

13.2 Oppositions

In presenting an opposition, a party shall set out in the following order:

(a) The evidence (i.e., a list in numerical order of all exhibits by number) upon which the opposing party relies in support of the opposition.

(b) Whether each fact alleged by the moving party is admitted, denied or that the opposing party is unable to admit or deny the fact alleged.

(c) Any additional facts upon which the opposing party intends to rely with a citation to the evidence.

(d) An argument stating the reason why relief is opposed shall be made in the following manner: "On page x, lines y-z of the motion, it is argued (or stated factually) that _____. The response is _____."

13.3 Replies

In presenting a reply, a party shall set out in the following order:

(a) The evidence (i.e., a list in numerical order of all exhibits by number) upon which the party relies for the first time in support of the reply.

(b) Whether each additional fact alleged by the opposing party is admitted, denied or that the moving party is unable to admit or deny the fact alleged.

(c) Any additional facts upon which the moving party intends to rely to rebut additional facts alleged by the opposing party with a citation to the evidence and an explanation as to why each additional fact was not set out in the motion.

(d) The argument responsive to statements in the opposition shall be made in the following manner: "On page x, lines y-z of the opposition, it is argued (or stated factually) that _____. The response is _____."

13.4 Specific preliminary motions

13.4.1 Preliminary motion--anticipation

When anticipation (35 U.S.C. 102) is the basis for a 37 CFR § 1.633(a) preliminary motion for judgment, each claim alleged to be anticipated shall be reproduced as an appendix to the 37 CFR § 1.633(a) preliminary motion.

Following each element or step recited in the claim, and within braces { }, there shall be inserted in bold a specific citation to the column and line or drawing figure and numeral or other material where a prior art reference describes each element or step recited in the claim. Braces { } are required instead of brackets [ ] because brackets have been used to indicate amended portions of claims in reissue applications.

This procedure shall be used for each claim of an opponent that a party maintains is anticipated.

13.4.2 Preliminary motion--obviousness

When obviousness (i.e., 35 U.S.C. 103) over the prior art is the basis for a 37 CFR § 1.633(a) preliminary motion for judgment, the claim annotation of ¶ 13.4.1 shall be used to indicate for each element or step in the claim where a prior art reference teaches or suggests the element or step in the claim. If the reference does not teach or suggest the element or step, that fact shall be explicitly identified as a difference.

An explanation shall be made in the body of the preliminary motion (not an appendix) as to why the subject matter of the claim, as a whole, would have been obvious to a person having ordinary skill in the art notwithstanding any difference.

This procedure shall be used for each claim of an opponent that a party maintains is unpatentable based on obviousness.

13.4.3 Preliminary motion--request for testimony

If a request is to be made for leave to take testimony (37 CFR § 1.639) to support a 37 CFR § 1.633 preliminary motion, opposition or reply, the request shall be made by a 37 CFR § 1.635 miscellaneous motion filed sufficiently before the 37 CFR § 1.633 preliminary motion, opposition or reply is due so the testimony (i.e., affidavit or transcript of any deposition) can be served with the 37 CFR § 1.633 preliminary motion, opposition or reply.

If a party knows that testimony will be needed to support a 37 CFR § 1.633 preliminary motion at the time of the conference call to set times for taking action during the preliminary motion phase, the administrative patent judge should be advised at that time.

If the motion is granted, testimony may be (1) *ex parte*, subject to subsequent cross-examination, or (2) *inter partes*. Therriault v. Garbe, 53 USPQ2d 1179 (Bd. Pat. App. & Int. 1999).

13.4.4 Preliminary Motion--inequitable conduct or fraud

The requirements of ¶ 13.10.1 of this STANDING ORDER are applicable to any 37 CFR § 1.633(a) preliminary motion for judgment based on alleged inequitable conduct or fraud.

A party must be in a position to make out a *prima facie* case of inequitable conduct or fraud at the time the 37 CFR § 1.633(a) preliminary motion is filed. Additional discovery (37 CFR § 1.687(c)) or a request to take testimony (37 CFR § 1.639(c)) of an opponent, asserted to be necessary to make out a *prima facie* case, generally will not be authorized. Filing of a 37 CFR § 1.633(a) preliminary motion based on alleged inequitable conduct or fraud that fails to

make out a *prima facie* case may result in sanctions or a referral to the Office of Enrollment and Discipline.

13.4.5 Motion to correct inventorship

Subject to the requirements of 37 CFR § 1.636(c), a 37 CFR § 1.634 motion to correct inventorship may be authorized at any time. The movant must initiate a conference call with the administrative patent judge and opposing counsel to obtain authorization.

Times for filing the motion, opposition and reply will be set by the administrative patent judge.

Appropriate action will be taken to minimize prejudice to a non-moving party in those cases where the motion is filed after the time for filing 37 CFR § 1.633 preliminary motions.

13.4.6 Preliminary motion--adding reissue application

A party filing a 37 CFR § 1.633(h) preliminary motion to add a reissue application to an interference must agree that all claims in the reissue application, not contained in the original patent, correspond to a count in the interference. See Winter v. Fujita, 53 USPQ2d 1234 (Bd. Pat. App. & Int. 1999), reh'g denied, 53 USPQ2d 1478 (Bd. Pat. App. & Int. 1999). A reissue application will not be added to an interference unless every added or amended claim is designated as corresponding to a count.

13.4.7 Preliminary motion--designating claims

A party's 37 CFR § 1.633(c) preliminary motion seeking to have its claim designated as corresponding to a count shall establish that the claim covers the same patentable invention as an opponent's claim that the party agrees corresponds to the count. A party's 37 CFR § 1.633(c) preliminary motion seeking to have its claim designated as not corresponding to a count shall establish that the claim covers an invention that is not the same patentable invention as any of the opponent's claims designated as corresponding to a count.

13.4.8 Preliminary motion--interference in fact

A party alleging that there is an interference-in-fact between its claim and a claim of an opponent must establish **both**:

(a) assuming the movant's claim is prior art to an opponent's claim, that the subject matter of the movant's claim would have anticipated (35 U.S.C. 102) or rendered obvious the subject matter of (35 U.S.C. 103) the opponent's claim **and**

(b) assuming the opponent's claim is prior art to the movant's claim, that the subject matter of the opponent's claim would have anticipated or rendered obvious the movant's claim.

13.5 Page number limitation on motions, oppositions and replies

A motion is limited to twenty-five (25) pages, not including any certificate of service.

An opposition to a motion is limited to twenty-five (25) pages, not including any certificate of service.

A reply to an opposition is limited to ten (10) pages, not including any certificate of service.

13.6 Combined oppositions and replies not to be filed

An opposition shall respond to only a single motion; "combined" oppositions responding to more than one motion shall not be filed.

A reply shall respond to only a single opposition; "combined" replies to more than one opposition shall not be filed.

One purpose of this requirement is to minimize the possibility that an argument will be overlooked.

13.7 New issues in replies

No new issues shall be raised in replies.

A reply may be deemed to have raised a new issue if the reply refers to new evidence that (1) is necessary to make out a *prima facie* case for the relief requested in the motion or (2) could have been included with the motion.

A reply that is longer than the corresponding motion and opposition probably raises new issues.

If a reply raises any new issue or belatedly relies upon evidence that should have been earlier presented, the entire reply and belatedly relied upon evidence will not be considered and may be returned. The board will not attempt to sort proper from improper portions of the reply.

An improper reply may be returned.

13.8 Prohibition against incorporation by reference

Arguments presented in one paper shall not be incorporated by reference to another paper.

The purpose of this requirement is to minimize the chance that an argument will be overlooked and to maximize the efficiency of the decision-making process. In this respect, the Trial Section adopts the rationale of the court in DeSilva v. DiLeonardi, 181 F.3d 865, 866-67 (7th Cir 1999) that incorporation of arguments by reference amounts to a self-help increase in the length of the brief and a pointless imposition on the board's time. A brief must make all arguments accessible to readers, rather than ask them to play archaeologist with the record.

13.9 Copies for oral argument

If oral argument is requested by either party, each party shall provide three sets of the party's motions. Each set should be filed in a separate box or accordion file with a separate folder for each motion. Each motion folder shall include a copy of the party's motion, a copy of the opposition, and a copy of the reply.

13.10 Miscellaneous motions (37 CFR § 1.635)

There are three kinds of motions that can be filed in an interference:

(a) A preliminary motion (37 CFR § 1.633).

(b) A motion to correct inventorship (37 CFR § 1.634).

(c) A miscellaneous motion (37 CFR § 1.635).

Any motion not filed under 37 CFR §§ 1.633 or 634 is a miscellaneous motion under 37 CFR § 1.635.

13.10.1 Conference call prior to filing contested miscellaneous motion

Prior to filing a 37 CFR § 1.635 miscellaneous motion, a party shall:

(a) confer with all opponents (37 CFR § 1.637(b)) and, if agreement cannot be reached,

(b) arrange a conference call to the administrative patent judge designated to handle the interference.

A motion for a clarification of procedure to be used in an interference shall not be filed until a conference call has been placed to the administrative patent judge designated to handle an interference.

The movant must explain why the motion is timely.

The parties, at their expense, may retain the services of a court reporter to record any conference call. A court reporter is often desirable inasmuch as an oral decision may be made with respect to issues raised during the conference call.

13.10.2 Time to respond to miscellaneous motions

The time for filing an opposition to a 37 CFR § 1.635 miscellaneous motion is **five (5) working days** after service of the motion. 37 CFR § 1.638(a).

The time for filing a reply to an opposition to a 37 CFR § 1.635 miscellaneous motion is **three (3) working days** after service of the opposition. 37 CFR § 1.638(b).

13.10.3 Specific miscellaneous motions

13.10.3.1 Suggestion to add an application or patent (37 CFR § 1.642)

The procedure applicable to 37 CFR § 1.635 miscellaneous motions shall apply to suggestions to add an application or patent to an interference (37 CFR § 1.642). Any suggestion shall:

(a) identify the additional application or patent proposed to be added;

(b) certify that a complete copy of the file wrapper of the application or patent has been served on all opponents;

(c) indicate which claims of the patent or application should be designated as corresponding to the count by explaining why there is an interference-in-fact between the claims of the patent or application sought to be added and the claims of the opponent's application or patent already involved in the interference; and

(d) explain whether there are alternative remedies; if so, why alternative remedies are not adequate; and what attempts, if any, have been made to have the examiner recommend declaration of another interference involving the application or patent sought to be added to the interference.

13.10.3.2 Motion for ruling on the admissibility of evidence

At any appropriate time, a party may file a 37 CFR § 1.635 miscellaneous motion (in limine) for a ruling on the admissibility of evidence.

13.10.3.3 Motion for additional discovery 37 CFR § 1.687(c)

At any appropriate time, a party may file a 37 CFR § 1.635 miscellaneous motion for additional discovery.

14 Submission of evidence

14.1 Objections

14.1.1 Time for objection to admissibility of evidence

Any objection to the admissibility of evidence, including evidence filed with any 37 CFR § 1.633 preliminary motion, opposition or reply, shall be served (but need not be filed) within **five (5) business days** of service of the evidence to which the objection is made.

14.1.2 Motion to exclude evidence

A motion to exclude evidence during the preliminary motion phase or priority phase (e.g., 37 CFR § 1.656(h)) of an interference shall:

(a) identify where in the record the objection was originally made and

(b) address objections to the exhibit (or part thereof) in numerical order.

The purpose of this section is to facilitate consideration of objections to exclude evidence. If an objection could have been made before the filing of supplemental evidence and an objection was not made, the objection is waived.

14.2 Time for serving supplemental evidence

Any supplemental evidence responding to any objection to the admissibility of evidence shall be served (but not filed) within **two (2) weeks** of the date an objection was served.

14.3 Time for cross-examination

Unless otherwise agreed, cross-examination of any affiant may begin no earlier than **twenty-one (21) days** after service of an affidavit.

A notice requesting cross-examination shall be served (but need not be filed).

Unless otherwise agreed, cross-examination of an affiant relied upon in a 37 CFR § 1.633 preliminary motion shall take place at least **ten (10) days** before an opposition to the 37 CFR § 1.633 preliminary motion is due.

Unless otherwise agreed, cross-examination of an affiant relied upon in an opposition to a 37 CFR § 1.633 preliminary motion shall take place at least **ten (10) days** before a reply is due.

A party relying on an affiant is obligated to have the affiant available for cross-examination during the time required by this STANDING ORDER. The party is also responsible for securing the services of a court reporter and providing a copy of any transcript to its opponent.

14.4 Order and place of cross-examination

The party requesting cross-examination, upon reasonable notice, may select the order in which cross-examination occurs when more than one witness is to be cross-examined.

Cross-examination shall take place at a reasonable location within the United States. Upon failure of the parties to agree to a place, date or time, a conference call shall be arranged with the administrative patent judge.

Cross-examination may be ordered to take place in the presence of the administrative patent judge. In the past, cross-examination has taken place before an administrative patent judge in cases where inventorship, derivation, or inequitable conduct has been an issue or where testimony is given through an interpreter.

14.5 Reliance on portion of a patent or application file

If a motion relies on any a paper in the file of an involved or benefit patent or application (including a specification or drawings), a copy of the entire paper shall be made an exhibit in the interference.

14.6 Specification as evidence

A specification of an application or patent involved in the interference is admissible as evidence only to prove what the specification or patent describes.

If there is data in the specification upon which a party intends to rely to prove the truth of the data, an affidavit by an individual having first-hand knowledge of how the data was generated (i.e., the individual who performed an experiment reported as an example in the specification) must be filed.

The individual may be cross-examined.

14.7 Affidavits in file wrappers not evidence

Affidavits, such as 37 CFR § 1.131 and 37 CFR § 1.132 affidavits, presented during *ex parte* prosecution of an involved or benefit application or patent are not evidence in an interference.

If a party seeks to have such an affidavit considered, the party must place the affidavit in evidence.

Any opponent will have an opportunity to object to the admissibility of the evidence and may cross-examine.

A party submitting the evidence will have an opportunity to supplement the evidence following a timely objection by an opponent.

14.8 Exhibits

All evidence (including affidavits, transcripts of depositions, documents and things) shall be presented as an exhibit.

An exhibit should ordinarily be a single document. Do **not** submit an entire application file as a single exhibit.

14.8.1 Numbering of exhibits

Exhibits used by a party in an interference shall be assigned consecutive numbers throughout the course of the interference.

Exhibits should be identified by an exhibit number (not letters) on a label placed in the lower right-hand corner of the first page of the exhibit. Compare 37 CFR § 1.653(i).

If important material is covered by an exhibit label on the first page of the exhibit, a copy of the first page of the exhibit shall be reproduced and presented as page 1-a of the exhibit.

Exhibits should be labeled, e.g., as follows:

Jones EXHIBIT 2001
Jones v. Smith
Interference 108,111

All exhibits shall be assigned an exhibit number.

The party initially designated as senior party shall consecutively number exhibits beginning with Exhibit 1001.

The party initially designated as junior party shall consecutively number exhibits beginning with Exhibit 2001.

Exhibits in a series above 2000 (i.e., 3000, 4000, etc.) are reserved for those interferences where there is more than one junior party.

14.8.2 Filing of exhibits

At an appropriate time during the preliminary motion phase and the priority testimony phase of an interference, the parties shall file a set of all original exhibits.

A set of original exhibits shall be submitted in an accordion folder, box or other folder containing all exhibits in numerical order, separated by a divider that conspicuously identifies each exhibit by number.

If oral argument is requested by any party, three separate additional sets of exhibits shall be filed.

If oral argument is not requested by any party, one additional set of exhibits shall be filed.

14.8.3 Record

Certified copies of depositions need not be filed unless required by the board.

The filing of exhibits as indicated in this section shall be deemed to constitute compliance with 37 CFR § 1.653.

14.8.4 Prohibition against multiple copies of same exhibit

The filing of multiple copies of the same exhibit with different exhibit numbers is not authorized.

14.8.5 Exhibit list

Each party shall maintain an exhibit list.

The exhibit list shall contain the exhibit number and a brief description of the exhibit.

The exhibit list shall be filed with the exhibits.

An up-to-date exhibit list shall be served whenever evidence is served.

14.9 Affidavits of expert witnesses

Affidavits expressing an opinion of an expert must disclose the underlying facts or data upon which the opinion is based. See Fed. R. Evid. 705 and 37 CFR §§ 1.639(b) and 1.671(b).

Opinions expressed without disclosing the underlying facts or data may be given little, or no, weight. See Rohm and Haas Co. v. Brotech Corp., 127 F.3d 1089, 1092, 44 USPQ2d 1459, 1462 (Fed. Cir. 1997) (nothing in the Federal Rules of Evidence or Federal Circuit jurisprudence requires the fact finder to credit the unsupported assertions of an expert witness).

Affidavits of patent law experts on issues of law generally will not be admitted in evidence.

14.10 Reliance on scientific tests and data

Parties often rely on scientific tests and data, both in the preliminary motion phase and during the priority testimony phase. Examples include IR (infra-red spectroscopy) and graphs generated therefrom, HPLC (high performance liquid chromatography) and data generated therefrom, etc.

In the event a party relies on a scientific test or data generated from a scientific test, the party relying on the test or data shall explain:

(a) the reason why the test is being used and why the data is being relied upon;

(b) how the test is performed;

(c) how the data is generated using the test;

(d) how the data is used to determine a value;

(e) the acknowledged accuracy of the test; and

(f) any other information that would aid the board in understanding the significance of the test or data.

Any explanation should take place through affidavit testimony of a witness, preferably accompanied by citation to relevant pages of standard texts (which should be exhibits in the interference).

14.11 Letters between counsel not to be filed

Unless a letter between counsel is made an exhibit to a motion, opposition, or reply, or during cross-examination, no letters between counsel are to be filed with the board.

15 Settlement and other agreements

15.1 Notice under 35 U.S.C. 135(c)

Notice is hereby given of the requirement of 35 U.S.C. § 135(c) for filing in the USPTO a copy of any agreement "in connection with or in contemplation of the termination of the interference." See Unisys Corp. v. Commissioner of Patents and Trademarks, 39 USPQ2d 1842 (D.D.C. 1993).

The date an interference terminates is set out in 37 CFR § 1.661.

15.2 Requirement for settlement negotiations

The parties are encouraged to attempt to settle interferences.

The purpose of this section is to facilitate settlement discussions.

To eliminate any possibility that initiation of settlement discussions might be construed as a weakness on the part of the party initiating settlement discussions, the senior party shall be responsible for (1) initiating any settlement discussions, (2) initially drafting any document and (3) initiating any conference call required by this section.

The parties may agree to permit a junior party to undertake the obligation placed upon the senior party by this section.

Within **three (3) months** of the date of the NOTICE DECLARING INTERFERENCE, the parties are required to conduct a settlement conference and discuss settlement possibilities.

The administrative patent judge designated to handle an interference may be contacted via conference call to render any appropriate assistance that might be needed to accomplish settlement.

Within **three (3) months** of the date of the NOTICE DECLARING INTERFERENCE, the parties are required to initiate a conference call with the administrative patent judge designated to handle an interference and should be prepared to discuss at that time:

(a) report on the outcome of the settlement conference;

(b) whether the parties are actively engaged in settlement negotiations and, if so, what steps have already been taken toward settlement;

(c) whether any settlement negotiations are directed toward resolving prior inventorship and obviating the need for filing 37 CFR § 1.633 preliminary motions;

(d) identify any issues that are not subject to settlement negotiations; and

(e) the status of any settlement negotiations, including how much time might be needed to conclude those negotiations.

Unless a different time is set in an order establishing a testimony period, within **two (2) months** after a decision on 37 CFR § 1.633 preliminary motions, the parties are further required to conduct a settlement conference and discuss settlement possibilities. Within the same time period, the parties are also required to initiate another conference call with the administrative patent judge designated to handle an interference and should be prepared to discuss at that time the items set out in subsections (a) through (e), *supra*.

Unless a different time is set in an order establishing a testimony period, within **one (1) month** after service of the priority record, the parties are still further required to conduct a settlement conference and discuss settlement possibilities. Within the same time period, the parties also are required to initiate another conference call with the administrative patent judge

designated to handle an interference and should be prepared to discuss at that time the items set out in subsections (a) through (e), *supra*.

Prior to initiating any conference call required by this section, the parties are required to file (preferably by facsimile) a joint statement indicating that a good faith effort has been made to settle the interference.

16 Guidelines for cross-examination

Cross-examination is a useful tool for determining the facts in a case. In interference cases, testimony is initially presented by affidavit. 37 CFR § 1.639(b); 37 CFR § 1.672(b) and (c).

Cross-examination occurs by oral deposition. 37 CFR § 1.672(d).

With respect to the cross-examination depositions, the guidelines of Hon. Robert S. Gawthrop, III, U.S. District Judge, essentially as set out in his opinion for the court in Hall v. Clifton Precision, 150 F.R.D. 525 (E.D. Pa. 1993), shall apply as hereinafter discussed. There is only one basic exception and that exception is due to USPTO rules. Certain objections must be noted on the record. See 37 CFR § 1.675(c).

As Judge Gawthrop notes, a deposition is meant to be a question-and-answer conversation between the deposing lawyer and the witness. There is no proper need for the witness's own lawyer to act as an intermediary, interpreting questions, deciding which questions the witness should answer, and helping the witness to formulate answers. The witness comes to the deposition to be questioned on cross-examination. It is the witness, and not the lawyer, who is the witness.

In view of the above, and pursuant to 37 CFR § 1.610(e), the following guidelines shall apply.

16.1 Guideline [1]

At the beginning of the deposition, deposing counsel taking cross-examination shall instruct the witness on the record to ask deposing counsel, rather than the witness's own counsel,

for clarifications, definitions or explanations of any words, questions or documents presented during the course of the deposition. The witness shall abide by the instructions.

16.2 Guideline [2]

Counsel shall not direct or request that a witness not answer a question, unless:

(a) counsel has objected to the question on the ground that the answer would:

(1) reveal privileged material or

(2) violate a limitation imposed by an administrative patent judge or a panel of the board and

(b) counsel immediately places a conference call to the administrative patent judge designated to handle an interference asking orally for a ruling on the objection.

Under these circumstances, (i) the deposition shall be suspended, (ii) the conference call immediately shall be placed to the administrative patent judge designated to handle an interference and (iii) all counsel must be prepared to address orally their respective positions. The court reporter in attendance at the deposition shall be available to record any telephone discussion and to read back questions to which an objection has been made.

If an administrative patent judge cannot be reached, then the party directing a witness not to answer shall, within **two (2) working days**, hand deliver to the board (¶ 1.3.3.1), and not to the USPTO Mail Room or any other USPTO office, a 37 CFR § 1.635 miscellaneous motion seeking relief. Any opposition must be hand delivered to the Board within **two (2) working** days. While a reply can be filed, counsel should assume that the motion is under advisement and can be decided (a) at any time upon receipt of an opposition or (b) immediately if no timely opposition is hand delivered to the board.

16.3 Guideline [3]

Counsel shall not make objections or statements that even remotely suggest an answer to a witness. Any objection to evidence during a deposition shall be stated concisely and in a non-argumentative and non-suggestive manner and must include the legal basis for the objection.

Opposing counsel should not address the correctness of an objection. Rather, opposing counsel should continue with questions to the witness, the objection having been noted on the record as required by 37 CFR § 1.675(c).

With respect to this guideline, the following observation by Judge Gawthrop is highly relevant:

> I also note that a favorite objection or interjection of lawyers is, "I don't understand the question; therefore the witness doesn't understand the question." This is not a proper objection. If the witness needs clarification, the witness may ask the deposing lawyer for clarification. A lawyer's purported lack of understanding is not a proper reason to interrupt a deposition. In addition, counsel are not permitted to state on the record their interpretations of questions, since those interpretations are irrelevant and often suggestive of a particularly desired answer.

By way of example, the following comments by counsel not conducting cross-examination generally are viewed as suggesting an answer to a witness:

(a) Objection, vague.

(b) Objection, to the form of the question.

(c) Take your time in answering the question.

(d) Look at the document before you answer.

(e) Counsel, do you want to show the witness the document?

16.4 Guideline [4]

Counsel and their witness-clients shall not engage in private, off-the-record conferences during depositions or during breaks or recesses, except for the purpose of deciding whether to assert a privilege. The term "witness-clients" in the context of this guideline and patent interference practice includes all witnesses who are employed by, or otherwise under the control

of, the real party in interest in the interference, including retained expert witnesses, as well as the individual or individuals named in the caption of the interference.

With respect to this guideline, the following observation by Judge Gawthrop is highly relevant:

> The fact that there is no [administrative patent] judge in the room to prevent private conferences does not mean that such conferences should or may occur. The underlying reason for preventing private conferences is still present: they tend, at the very least, to give the appearance of obstructing the truth.

16.5 Guideline [5]

Any conferences that occur pursuant to, or in violation of, guideline [4] are a proper subject for inquiry by deposing counsel to ascertain whether there has been any witness-coaching and, if so, the nature of that coaching.

16.6 Guideline [6]

Any conferences that occur pursuant to, or in violation of, guideline [4] shall be noted on the record by the counsel who participated in the conference. The purpose and outcome of the conference shall also be noted on the record.

16.7 Guideline [7]

Deposing counsel taking cross-examination shall provide to the witness's counsel a copy of all documents shown to the witness during the deposition. The copies shall be provided either before the deposition begins or contemporaneously with the showing of each document to the witness. The witness and the witness's counsel do not have a right to discuss documents privately before the witness answers questions about the documents.

16.8 Sanction

Failure to adhere strictly to these guidelines may be a basis for a sanction under 37 CFR § 1.616, which could include a requirement that the witness, on very short notice (i.e., the next day including, if appropriate, a non-work day) may be directed to appear before an administrative

patent judge in Arlington, Virginia or elsewhere as may be appropriate, coupled with any appropriate award of compensatory damages under 37 CFR § 1.616. In addition, cross-examination undertaken contrary to these guidelines may result in exclusion of an affidavit from evidence or little, if any weight, being given to the direct testimony of a witness who was cross-examined.

17 **Comments on requests for extensions of time**

The parties are advised that times are set with the view to rendering prompt and timely decisions. Thus, in setting times in an interference, times set in other interferences and decisions that need to be rendered in the interference, as well as other interferences, are also taken into account.

A request for an extension of time is authorized by 37 CFR § 1.645. But, 37 CFR § 1.645 requires a showing of "good cause." Whatever a party's experience may be in other USPTO matters, prior interferences or courts generally, the standard of what constitutes "good cause" within the meaning of 37 CFR § 1.645 is high.

There are few, if any, circumstances where "good cause" can be based on the press of other business arising after a time is set by an order entered in an interference, particularly where a time period is set after conference with counsel. Thus, a matter in another case (i.e., argument or a trial) or an event (i.e., a deposition, client meeting in the U.S. or abroad, a vacation, etc.) scheduled or ordered after a conference call setting times in an interference, generally will not constitute grounds for an extension of time.

Generally, an attempt to settle is not "good cause." While settlement is encouraged, and the administrative patent judge designated to handle an interference is available to assist in settlement efforts where appropriate, the parties should expect either to settle the interference or, in the absence of settlement, to meet the next pending deadline.

18 Testimony through an interpreter

A conference call shall be placed to the administrative patent judge designated to handle the interference **at least five (5) business days** before testimony is to take place when the witness will give direct or cross-examination testimony through an interpreter. The conference call shall be initiated by the party who called the witness.

19 Oral argument

19.1 Visual aids at oral argument

Visual aids to be used at oral argument must be served no less than **three (3) business days** before oral argument.

Four copies (one for the record and one for each judge) must be presented at oral argument.

Any special equipment needed for oral argument is the responsibility of the party needing the equipment.

19.2 Transcript of oral argument

A party, at its expense, may retain the services of a court reporter to transcribe oral argument.

When an argument is to be transcribed, the party should notify Trial Section support staff personnel at least one business day prior to oral argument so that arrangements may be made in the hearing room for the reporter.

The court reporter shall use a steno machine and may also use a tape recording device as a backup. Microphones at individuals' locations are not authorized.

20 Decisions

20.1 Three-judge decisions govern further proceedings

An interlocutory order (37 CFR § 1.601(q)) entered by a panel consisting of three or more administrative patent judges generally governs further proceedings in an interference.

20.2 Request for reconsideration

20.2.1 Reconsideration of interlocutory orders

A party may request reconsideration of any interlocutory order (37 CFR § 1.640(c)).

A party may request review at final hearing of any interlocutory order (37 CFR § 1.655(a)), but the panel that will conduct the review generally will be the same panel that entered the interlocutory order even if other issues at final hearing are determined by a separate panel. Accordingly, the most efficient way to seek review of an interlocutory order entered by a panel is through a request for reconsideration.

20.2.2 Form for request

In requesting reconsideration of a decision, a party shall set out in the following order:

(a) The evidence (i.e., a list in numerical order of all exhibits by number) that the party believes was overlooked or misapprehended (37 C.F.R. §§ 1.640(c) and 1.658(b)). Evidence not already of record at the time of the decision will not be admitted absent a showing of good cause for the belated submission (37 C.F.R. § 1.645(b)).

(b) The argument responsive to the decision shall be made with particularity in the following manner: "On page _, lines _-_, the decision states _____. The decision is believed to have overlooked (or misapprehended) _____. This point was set forth in ___ Motion (or Opposition or Reply) _ at page _, lines _-_."

20.2.3 Number of requests

No more than one request for reconsideration may be filed per party per board decision.

21 Modification of STANDING ORDER

When appropriate, the terms of this STANDING ORDER may be modified by an administrative patent judge.

BRUCE H. STONER, JR., Chief
Administrative Patent Judge

RICHARD E. SCHAFER
Administrative Patent Judge

JAMESON LEE
Administrative Patent Judge

RICHARD TORCZON
Administrative Patent Judge

CAROL A. SPIEGEL
Administrative Patent Judge

SALLY GARDNER LANE
Administrative Patent Judge

SALLY C. MEDLEY
Administrative Patent Judge

MICHAEL P. TIERNEY
Administrative Patent Judge

MARK NAGUMO
Administrative Patent Judge

TRIAL SECTION

BOARD OF PATENT APPEALS AND INTERFERENCES

ORDER SETTING TIMES
(Times for taking action--preliminary motion phase)

A. Conference call

A @hearing/telephone conference call was held on @_____ @__, 19@__, at approximately @__:__ a/p.m., involving:

1. @_____, Esq., counsel for @_____.
2 @_____, Esq., counsel for @_____.
3. @_____, Administrative Patent Judge.

B. Relevant discussion during conference call

The principal purpose of the conference call was to set times for taking action during the preliminary motion phase of the interference.

@insert any relevant discussion not otherwise covered herein.

C. Time periods associated with preliminary motions

In accordance with discussion during the @hearing/telephone conference call, the TIME PERIODS described below are set out in an Appendix to this ORDER.

The parties are authorized to stipulate different times (earlier or later, but not later than TIME PERIOD 7) for TIME PERIODS 1 through 6, provided, a notice is filed with the board as soon as practical after any agreement is reached. The notice should be in the form of a photostatic copy of the Appendix attached to this ORDER with old dates crossed out and new dates inserted by hand (which helps the board determine the changes the parties have stipulated). The parties may not stipulate an extension of TIME PERIODS 7 or 8.

In stipulating different times, the parties also will need to consider adjustments to times to (1) object to evidence (5 business days--STANDING ORDER ¶ 14.1.1), (2) correct evidence (14 days--STANDING ORDER ¶ 14.2), (3) begin cross-examination (no earlier than 21 days after motion, opposition or reply is filed--STANDING ORDER ¶ 14.3) and (4) conclude cross-examination (at

least 10 days before opposition or reply is due--STANDING ORDER ¶ 14.3).

1. TIME PERIOD 1

By the end of TIME PERIOD 1:

a. File and serve all preliminary motions and

b. Serve but do not file evidence in support of those preliminary motions OR

c. If no party files a preliminary motion, arrange a conference call to the administrative patent judge so that appropriate adjustments to the schedule may be made.

2. TIME PERIOD 2

By the end of TIME PERIOD 2:

a. File and serve preliminary motions pursuant to 37 CFR § 1.633(i) and (j) responsive to a preliminary motion filed by an opponent during TIME PERIOD 1 and

b. Serve but do not file evidence in support of those responsive preliminary motions.

3. TIME PERIOD 3

By the end of TIME PERIOD 3:

a. File and serve oppositions to all preliminary motions, including responsive preliminary motions filed pursuant to 37 CFR § 1.633(i) and (j) and

b. Serve but do not file evidence in support of those oppositions.

4. TIME PERIOD 4

By the end of TIME PERIOD 4:

a. File and serve replies to all oppositions and

b. Serve but do not file evidence in support of those replies.

5. TIME PERIOD 5

By the end of TIME PERIOD 5, file and serve:

a. Any request for oral argument on preliminary motions,

b. Miscellaneous motions to exclude as inadmissible evidence relied upon by an opponent in connection with preliminary motions [compare 37 CFR § 1.656(h)] and

c. Observations by a cross-examining party with respect to cross-examination of an opponent's affiants that took place following filing of replies.

6. TIME PERIOD 6

By the end of TIME PERIOD 6, file and serve:

a. Oppositions to an opponent's motion to exclude evidence and

b. Any response to observations by a cross-examining party with respect to cross-examination of an opponent's affiants following filing of replies.

7. TIME PERIOD 7

By the end of TIME PERIOD 7, file and serve replies to oppositions to motions to exclude evidence.

D. Deposition transcripts

Transcripts of depositions of cross-examination and depositions taken under 35 U.S.C. § 24 shall be served, but not filed with the board until the exhibits are filed.

A certified copy of a transcript of a deposition need not be filed unless requested by the board.

E. Serving exhibits relied upon in preliminary motions

An exhibit, including an affidavit, relied upon in connection with preliminary motions, oppositions, and replies shall be served but not filed with the preliminary motion, opposition, reply or affidavit in which the exhibit is first

mentioned.[1]

F. TIME PERIOD 8: Time for filing the record in connection with preliminary motions

By the end of TIME PERIOD 8, file

1. An original and one or three sets of all exhibits (see STANDING ORDER ¶ 14.8.2);
2. For each preliminary or other motion, three folders each containing a set of motion documents, consisting of:
   a. The preliminary or other motion,
   b. Its opposition,
   c. Its reply,
   d. Any observations on cross-examination and
   e. Any response to the cross-examination observations.
3. Any ZIP® 100 Mb disk or CD-Rom a party elects to file.

G. Preliminary statements

1. By the of TIME PERIOD 1:
   a. File but do not serve preliminary statements [37 CFR § 1.621(a), see also 37 CFR § 1.626(a)].
   b. File and serve the notice required by 37 CFR § 1.621(d).
2. A junior party who does not file a preliminary statement shall not have access to the preliminary statement of any other party. 37 CFR § 1.631(b).
3. **Within one (1) week** after TIME PERIOD 1, serve a copy of the preliminary statement upon an opponent who served a notice under 37 CFR § 1.621(d).

---

[1] In order to permit an expedited decision, when an expedited schedule is set for a particular motion, all exhibits (including affidavits) mentioned in the motion, opposition or reply should be filed with the motion, opposition or reply in which the exhibit is first mentioned.

H. Oral argument

If appropriate, the date for oral argument on preliminary motions will be set upon receipt of requests for oral argument (see TIME PERIOD 5).

I. Signature

Administrative Patent Judge

@Date: _____
Arlington, VA
ORDERPM8 (Revised 27 January 2004)

Appendix--ORDER SETTING TIMES
(Times for taking action--preliminary motion phase)

Interference @105,___

1. TIME PERIOD 1 @_____
   Filing preliminary motions and preliminary statements

2. TIME PERIOD 2 @_____
   Filing Rule 633(i) and Rule 633(j) preliminary motions

3. TIME PERIOD 3 @_____
   Filing of oppositions to all preliminary motions

4. TIME PERIOD 4 @_____
   Filing of replies

5. TIME PERIOD 5 @_____
   Filing of request for oral argument; motions to suppress and observations with respect to cross-examination taken after filing of replies

6. TIME PERIOD 6 @_____
   Filing of oppositions to motions to suppress and any response to observations with respect to cross-examination

7. TIME PERIOD 7 @_____
   Filing replies to oppositions to motions to suppress

8. TIME PERIOD 8 @_____
   Filing exhibits, sets of preliminary motions and zip/CD-ROMs

ORDER SETTING TIMES
(Times for taking action--priority phase)

A. Conference call

A @hearing/telephone conference call was held on @_____ @__, 19@__, at approximately @__:__ a/p.m., involving:

2. @_____, Esq., counsel for @_____.
3. @_____, Esq., counsel for @_____.
3. @_____, Administrative Patent Judge.

B. Relevant discussion during conference call

The principal purpose of the conference call was to set times for taking action during the priority phase of the interference.

@insert any relevant discussion not otherwise covered herein.

C. Time periods associated with priority

In accordance with discussion during the @hearing/telephone conference call, the TIME PERIODS described below are set out in an Appendix to this ORDER.

The parties are authorized to stipulate different times (earlier or later, but not later than TIME PERIOD 17) for TIME PERIODS 11 through 16, provided, a notice is filed with the board as soon as practical after any agreement is reached. The notice should be in the form of a photostatic copy of the Appendix attached to this ORDER with old dates crossed out and new dates inserted by hand (which helps the board determine the changes the parties have stipulated). The parties may not stipulate an extension of TIME PERIODS 17 or 18.

In stipulating different times, the parties also will need to consider adjustments to times to (1) object to evidence (5 business days--STANDING ORDER ¶ 14.1.1), (2) correct evidence (14 days--STANDING ORDER ¶ 14.2), (3) begin cross-examination (no earlier than 21 days after principal, opposition or reply brief

is filed--STANDING ORDER ¶ 14.3) and (4) conclude cross-examination (at least 10 days before opposition or reply is due--STANDING ORDER ¶ 14.3).

1. TIME PERIOD 11

By the end of TIME PERIOD 11 the junior party shall:

a. File and serve a principal brief on the issue of priority

and

b. Serve <u>but do not file</u> evidence in support of the junior party's priority case OR

c. If the junior party does not file a principal brief, arrange a conference call to the administrative patent judge so that appropriate action may be taken.

2. TIME PERIOD 12

By the end of TIME PERIOD 12, the senior party shall:

a. File and serve a principal brief on the issue of priority

and

b. Serve <u>but do not file</u> evidence in support of the senior party's priority case.

3. TIME PERIOD 13

By the end of TIME PERIOD 13:

a. File and serve opposition briefs to all priority cases and

b. Serve <u>but do not file</u> evidence in support of those oppositions.

4. TIME PERIOD 14

By the end of TIME PERIOD 14:

a. File and serve replies to all oppositions to priority cases and

b. Serve <u>but do not file</u> evidence in support of those replies.

5. TIME PERIOD 15

By the end of TIME PERIOD 15, file and serve:

a. Any request for oral argument on priority,

b. Miscellaneous motions to exclude as inadmissible evidence relied upon by an opponent in connection with priority [compare 37 CFR § 1.656(h)],

c. Observations by a cross-examining party with respect to cross-examination of an opponent's affiants that took place following filing of replies and

d. A list of issues other than priority which are to be considered in rendering a final decision in the interference (there is no need to list an issue previously resolved by a decision entered by a 3-judge panel inasmuch as those decisions merge with the judgment when a final decision is entered).

6. TIME PERIOD 16

By the end of TIME PERIOD 16, file and serve:

a. Oppositions to an opponent's motion to exclude evidence and

b. Any response to observations by a cross-examining party with respect to cross-examination of an opponent's affiants following filing of replies.

7. TIME PERIOD 17

By the end of TIME PERIOD 17, file and serve replies to oppositions to motions to exclude evidence.

D. Deposition transcripts

Transcripts of depositions of cross-examination and depositions taken under 35 U.S.C. § 24 shall be served, but not filed with the board until the exhibits are filed.

A certified copy of a transcript of a deposition need not be filed unless requested by the board.

E. Serving exhibits relied upon in priority

An exhibit, including an affidavit, relied upon in connection with priority shall be served but not filed with the principal, opposition or reply brief in which the exhibit is

first mentioned.

F. TIME PERIOD 18: Time for filing the record in connection with priority

By the end of TIME PERIOD 18, file

1. An original and one or three sets of all exhibits (see STANDING ORDER ¶ 14.8.2);
2. For each case for priority, three folders each containing a set of motion documents, consisting of:
   a. The principal brief,
   b. Its opposition,
   c. Its reply,
   d. Any observations on cross-examination and
   e. any response to the cross-examination observations.
3. Any ZIP® 100 Mb disk or CD-Rom a party elects to file.

G. Reserved

H. Oral argument

If appropriate, the date for oral argument on priority will be set upon receipt of requests for oral argument (see TIME PERIOD 15).

I. Signature

_____

Administrative Patent Judge

@Date: _____
Arlington, VA
ORDERTE8 (Revised 27 January 2004)

Appendix--ORDER SETTING TIMES
(Times for taking action--priority motion phase)

Interference @105,___

11. TIME PERIOD 11 @_____
Filing junior party priority principal brief

12. TIME PERIOD 12 @_____
Filing senior party priority principal brief

13. TIME PERIOD 13 @_____
Filing of oppositions to all principal briefs

14. TIME PERIOD 14 @_____
Filing of replies to all oppositions

15. TIME PERIOD 15 @_____
Filing of request for oral argument; motions to suppress; observations with respect to cross-examination taken after filing of replies; issues to be considered in entering final decision

16. TIME PERIOD 16 @_____
Filing of oppositions to motions to suppress and any response to observations with respect to cross-examination

17. TIME PERIOD 17 @_____
Filing replies to oppositions to motions to suppress

18. TIME PERIOD 18 @_____
Filing exhibits, sets of priority briefs and zip/CD-ROMs

Preliminary Motions--Default times for taking action

Enter					
Declaration date	03/29/04				
	Calculate Date	Enter Weeks	Calculate Days		Description
Declaration	03/29/04	0	0		
Real party	04/12/04	2	14		
Request for file	04/12/04	2	14		
Clean copy claims	04/12/04	2	14		
Means analysis	04/26/04	4	28		
Drawing analysis	04/26/04	4	28		
P/M list	05/22/04				
Conference Call	05/24/04	8	56		
Time Period 1	07/05/04	6	42		Preliminary motions due
Object evidence	07/12/04		7	1	
Correct evidence	07/26/04		14	2	
Time Period 2	07/26/04	3	21		I & j preliminary motions
Object evidence	08/02/04		7	1	
Correct evidence	08/16/04		14	2	
Cross can begin	08/16/04		21	3	
Cross must end	08/27/04				
Time Period 3	09/06/04	6	42		Oppositions due
Object evidence	09/13/04		7	1	
Correct evidence	09/27/04		14	2	
Cross can begin	09/27/04		21	3	
Cross must end	10/08/04				
Time Period 4	10/18/04	6	42		Replies due
Object evidence	10/25/04		7	1	
Correct evidence	11/08/04		14	2	
Cross can begin	11/08/04		21	3	
Cross must end	11/19/04				
Time Period 5	11/29/04	6	42		Request for hearing, motion to suppress and & x-exam observations
Time Period 6	12/20/04	3	21		Suppression opposition & response to observations
Time Period 7	01/03/05	2	14		Suppression reply
Time Period 8	01/10/05	1	7		File record
Oral argument 9	02/07/05	4	28		Oral argument
P/m decision 10	03/14/05	5	35		Decision on p/m

Total Weeks from conference call to Time Period 8	33
Total weeks from declaration to Time Period 8	41
Total weeks from declaration to decision on p/m	50

Priority--default times

Enter
Decision on p/m 03/14/05

		Calculate Date	Enter Weeks	Calculate Days		Description
Conference Call		04/11/05	4	28		
Time Period	11	**05/23/05**	6	42		Junior priority & brief
Object evidence		05/30/05		7	1	
Correct evidence		06/13/05		14	2	
Time Period	12	**07/04/05**	6	42		Senior priority & brief
Object evidence		07/11/05		7	1	
Correct evidence		07/25/05		14	2	
Cross can begin		07/25/05		21	3	
Cross must end		08/05/05				
Time Period	13	**08/15/05**	6	42		Opposition & brief
Object evidence		08/22/05		7	1	
Correct evidence		09/05/05		14	2	
Cross can begin		09/05/05		21	3	
Cross must end		09/16/05				
Time Period	14	**09/26/05**	6	42		Rebuttal & brief due
Object evidence		10/03/05		7	1	
Correct evidence		10/17/05		14	2	
Cross can begin		10/17/05		21	3	
Cross must end		10/28/05				
Time Period	15	**11/07/05**	6	42		Request for hearing, motion to suppress and & x-exam observations
Time Period	16	**11/28/05**	3	21		Suppression opposition & response to observations
Time Period	17	**12/12/05**	2	14		Suppression reply
Time Period	18	**12/19/05**	1	7		File record
Oral argument	19	**01/16/06**	4	28		Oral argument
Priority decision	20	**02/20/06**	5	35		Decision on priority

Total Weeks from conference call to Time Period 18	36
Total weeks from p/m decision to Time Period 18	40
Total weeks from p/m decision to priority decision	49

a

BoxInterferences@USPTO.GOV
Tel: 703-308-9797
Fax: 703-305-0942

ORDER
(Electronic filing/pilot project)

I. Policy

A. The purpose of this pilot project is:

1. To speed communications,
2. To reduce costs of communications,
3. To increase reliability in the face of unusual postal disruptions,
4. To implement various administrative and legislative policies for providing the option of electronic filing, and
5. To identify other benefits, as well as to correct problems, that may arise during the course of the pilot project.

B. Participation is voluntary, but electronic filing is encouraged. A participant may opt out of the program but must initiate a teleconference with the administrative patent judge and the opposing party to provide notice.

C. Switching between modes of communication (i.e., e-filing versus paper filing (including faxing)) is not permitted. As long as a party is in the program, it should only file electronically except as provided below.

II. Format

A. All papers, excluding exhibits, should be filed in Adobe® portable document format (pdf). This requirement is necessary to ensure standardization and consistent pagination regardless of the user's hardware and software.

B. Each paper (not each page) should be a separate pdf file.

C. Exhibits may be filed in either paper or pdf, although any reasonable efforts to provide a pdf copy is encouraged.

D. The Board prefers that papers be filed in **text-searchable** pdf whenever reasonably possible. Newer versions of Corel® WordPerfect® provide this translation capacity as a built-in feature. Adobe Acrobat® software provides this conversion capability for other word processors.

E. A pdf paper filed by a registered practitioner must have a signature block indicating the responsible practitioner, but need not have an actual signature **provided** the paper is electronically filed from a mail address at the counsel's company or firm (currently @____.com and @____.com, respectively, e.g., jones.com and smith.com). Compliance with this provision will be deemed to be in compliance with 37 C.F.R. § 10.18.

F. Other documents requiring an original signature must be in image (scanned) format.

G. The STANDING ORDER requirements for formatting (paper size, etc.) remain in effect even for pdf papers, but (i) first pages need not be pink (¶ 3.1), (ii) an additional judge's copy need not be filed (¶ 3.2), and (iii) two holes at the top of the paper are not required (¶ 3.4).

H. Counsel are responsible for the accuracy of pdf files. Thus, counsel should review the pdf file to ensure that scanning or translation has not produced errors. In particular, translation can produce unexpected results for special characters (e.g., foreign characters and "curly" quote marks)

and for unusual fonts. Misfed or misoriented papers can produce problems in scanning.

III. Filing

A. The provisions of other orders in this interference continue to apply to papers filed in paper. Similarly, the timeliness of electronic files delivered by conventional (non-electronic mail) means is governed by those orders.

B. Papers, other than exhibits, filed electronically must be:

1. Electronically mailed to

BoxInterferences@USPTO.GOV

(Note that "BoxInterferences" is a single, plural word, but is not case sensitive.)

2. Only include "@_____(interference number)@_____(APJs initials)" (without a comma) in the subject line (e.g., 107000 SCM).

3. No papers unrelated to this interference should be filed at this electronic mail box without express written authorization from the APJ.

4. Note that this is the **only** in-box for filing. Do not send replies to InterferenceTrialSection@USPTO.GOV (the Trial Section's official out-box).

Sending one paper per electronic mail message is helpful to the Board's support staff. The electronic mail message transmitting the paper should be treated as a facsimile coversheet. No information except the title of the paper should be included in the body of the e-mail.

C. Exhibits filed with the record may be electronically mailed or otherwise delivered in any of the following PC-compatible media:

1. A compact disc,
2. 3¼ inch diskette,
3. A 100 MB Zip® disk, or
4. A 2 GB Jaz® disk.

Counsel should, of course, exercise common sense in choosing the mode of filing with due consideration for the difficulties inherent in filing very large files via electronic mail. Files larger than **one megabyte** (1Mb) tend to overload the USPTO mail server. Files larger than **three megabytes** (3Mb) will be rejected by the USPTO mail server. [Note that the new Standing Order **eliminates** the requirement for filing authorities]. Counsel should make every effort to submit files that are less than **one megabyte** (1Mb). Scanned documents tend to create very large files. Text files can be converted directly into text-searchable pdf files using Acrobat Distiller® or other conversion software. Such files tend to be much more compact than scanned files. Moreover, files may be compressed in Zip format for the purposes of filing, but may only be served in this format if opposing counsel has the ability to decompress (unzip) such files.

D. Papers mailed electronically will be considered timely if they are received at the Board (as determined by the Board's date stamp) no later than 10 a.m. (Eastern) of the business day following the due date for the paper (the nominal filing date). The use of return receipts are encouraged. The

provisions of other orders govern the timeliness of electronic media delivered by conventional means.

E. The electronic mail message accompanying the papers should indicate in the body of the message the papers being filed. For example, "JONES PRELIMINARY MOTION 1".

IV. Service

A. When papers are served in paper format, the provisions of other orders in this interference continue to apply. Similarly, when service of electronic media is accomplished by conventional delivery means, the provisions of the timeliness provisions of the other orders apply.

B. Service should be made by a method calculated to effect delivery within one business day of the nominal filing date for the paper.

C. Service will not be considered effective if the paper is served on an electronic medium that opposing counsel is not equipped to read. Hence, the parties should identify in advance the preferred modes of service. The default is service in paper format.

D. No certificate of service will be required if opposing counsel is included in the "cc" line of the electronic filing. If service is effected by conventional delivery means, the existing practice of incorporating the certificate in the paper should be used. If service is accomplished by a separate electronic mail message, an electronic mail message should be filed so stating, with a "cc" to opposing counsel.

Order--Authorizing submission of evidence on DVDs/pilot project

1. Purpose

The purpose of the pilot project is to put the parties on notice that they are authorized to submit, as exhibits, videos in DVD (digital video disc) format. The DVD may result from a deposition, recording of an experiment or such other event as may be appropriate.

2. Paper copies

The required number of paper copies of exhibits must also be filed with the board and served on all opponents. For example, a party submitting a DVD of a video deposition must also submit a paper copy of the transcript.

3. Format

(a) The board will not consider DVDs it cannot play.

(b) The board understands that DVDs encoded in MPEG-2 allows the DVD to be played on a set top DVD player and certain computers.

(c) The board has computer capability that will play DVDs encoded in MPEG-2.

(d) The board has computer capability to support DVD R media.

(e) The DVD must be indexed (e.g., title and chapter numbers) so that reference to and viewing of a particular portion of the video may be made.

(f) Any references to a DVD exhibit must specifically refer to a particular portion in the DVD (e.g., title number and chapter number) much like referring to a particular page and line number in a paper transcript.

(g) Any party wishing to file a DVD must provide four (4) copies of the DVD to the board.

(h) One copy of the DVD must be served on all opponents.

4. View of witness

Any DVD of a deposition must show only the head and upper torso of the witness.

Except for breaks, the DVD must contain the entire deposition of the witness. For example, the DVD should show whether the witness took a long time to answer a particular question or had to review documents unless review of documents takes place off the record during a break.

5. Costs

The following criteria applies to costs:

(a) A party recording an experiment or other event is responsible for all costs of making the DVD.

(b) A party calling the witness (i.e., the party who presented an affidavit of the witness) is responsible for the costs of any court reporter and required transcripts.

(c) If the party calling the witness wishes to have a DVD of cross-examination, the party is responsible for all costs of making the DVD.

(d) If the party calling the witness does not wish to have a DVD, but the opponent wishes to have a DVD of cross-examination, the opponent is responsible for all costs of making the DVD.

(e) If the opponent causes a deposition to be video recorded and later changes its mind on having a DVD prepared, the party calling the witness may cause the DVD to be prepared and shall be responsible for costs of having the DVD prepared.

(f) The parties are authorized to divide the costs of making a DVD in any proportion upon which they might agree.

6. Notice of intent to present DVD

If the party calling the witness intends to prepare a DVD of cross-examination, the party shall serve a notice of intent to prepare a DVD on the opponent five business days before the date of the deposition.

If the opponent intends to prepare a DVD and has not heard from the party, the opponent shall serve a notice of intent to prepare a DVD on the party three business days before the date of the deposition.

7. Live testimony

Nothing in this order precludes the board from indicating to the parties that in a particular instance it would prefer to have live testimony before one or more administrative patent judges. See ¶ 14.4 of the Standing Order.

PTO-850-(Rev. 9-27-95)

INTERFERENCE INITIAL MEMORANDUM

Count #_____

BOARD OF PATENT APPEALS AND INTERFERENCES: An interference is found to exist between the following cases:

This interference involves _____ parties

105208

PARTY	SERIAL NO.	FILING DATE	PATENT NO., IF ANY	ISSUE DATE, IF ANY
GRAY ET AL.	10/608,092	6-30-03	N/A	N/A

If application has been patented, have maintenance fees been paid? ___Yes ___No ___Maintenance fees not due yet

**Accorded the benefit of:

COUNTRY	SERIAL NO.	FILING DATE	PATENT NO., IF ANY	ISSUE DATE, IF ANY
See attached list				

The claim(s) of this party which correspond(s) to this count is(are):

PATENTABLE CLAIMS: 127-143 — UNPATENTABLE CLAIMS: NONE

The claim(s) of this party which does(do) not correspond to this count is(are):

PATENTABLE CLAIMS: NONE — UNPATENTABLE CLAIMS: NONE

PARTY	SERIAL NO.	FILING DATE	PATENT NO., IF ANY	ISSUE DATE, IF ANY
DIETZ-BAND ET AL.	09/170,630	10-13-98	6,414,133	7-2-02

If application has been patented, have maintenance fees been paid? ___Yes ___No ☒ Maintenance fees not due yet

**Accorded the benefit of:

COUNTRY	SERIAL NO.	FILING DATE	PATENT NO., IF ANY	ISSUE DATE, IF ANY

The claim(s) of this party which correspond(s) to this count is(are):

PATENTABLE CLAIMS: 1-3, 5-12, and 14-19 — UNPATENTABLE CLAIMS: NONE

The claim(s) of this party which does(do) not correspond to this count is(are):

PATENTABLE CLAIMS: 4 and 13 — UNPATENTABLE CLAIMS: NONE

Instructions

1. For every patent involved in the interference, check if the fees have been paid by using the **patent number** with the PALM screen CR06. If fees are due and they have not been paid, the interference cannot be declared since it would invovlve an expired patent. (35 USC 135(a); 37 CFR 1.606).
2. For each party, separately identify the patentable and unpatentable claims which correspond to the count. (37 CFR 1.601 (f), 1.601 (n), 1.609(b)(2)).
3. For each party, separately identify the patentable and unpatentable claims which do not correspond to the count (37 CFR 1.609(b)(3)).
4. Forward all files including those the benefit of which is being accorded.
5. Keep a copy of the Interference Initial Memorandum and any attachments for your records.

All information requested below must be attached on (a) separate sheet(s) and type-written.

6. On a separate sheet, set forth a single proposed interference count. If any claim of any party is exactly the same word for word as this count, please indicate the party, application or patent number, and the claim number.
7. For each claim designated as corresponding to the count, provide an explanation of why each claim defines the same patentable invention (37 CFR 1.609(b)(2)).
8. For each claim designated as not corresponding to the count, provide an explanation of why each claim defines a separate patentable invention (37 CFR 1.609(b)(3)).
9. For each additional count, if any, repeat steps 2-6 and, additionally, provide an explanation why each count represents a separate patentable invention from every other count (37 CFR 1.609(b)(1)).

DATE	PRIMARY EXAMINER (Signature)	TELEPHONE NO.	ART UNIT
2-17-04	Adam J. Basinski	(571) 272-0718	1631
DATE	GROUP DIRECTOR SIGNATURE (if required)		
2/25/04	Gary Kunz	571-272-0567.	

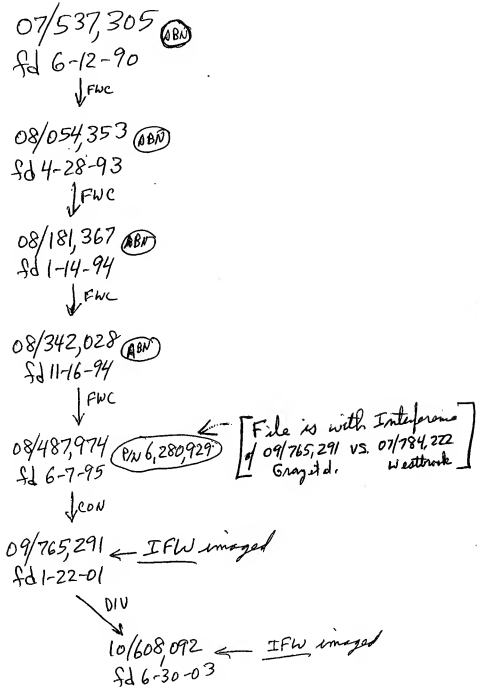
**The serial number and filing date of each application the benefit of which is intended to be accorded must be listed. It is not sufficient to merely list the earliest application if there are intervening applications necessary for continuity.

THIS PAGE CAN BE DUPLICATED IF THERE ARE MORE THAN TWO INTERFERING PARTIES.

GRAY ET AL. - Benefit applications

COUNTRY	SERIAL NO.	FILING DATE	PATENT NO., IF ANY	ISSUE DATE, IF ANY
U.S.	09/765,291	JANUARY 22, 2001	N/A	N/A
U.S.	08/487,974	JUNE 7, 1995	6,280,929	AUGUST 28, 2001
U.S.	08/342,028	NOVEMBER 16, 1994	N/A	N/A
U.S.	08/181,367	JANUARY 14, 1994	N/A	N/A
U.S.	08/054,353	APRIL 28, 1993	N/A	N/A
U.S.	07/537,305	JUNE 12, 1990	N/A	N/A

GRAY ET AL.


07/537,305
ABN
fd 6-12-90
FWC
08/054,353
ABN
fd 4-28-93
FWC
08/181,367
ABN
fd 1-14-94
FWC
08/342,028
ABN
fd 11-16-94
FWC
08/487,974
P/N 6,280,929
fd 6-7-95
File is with Interference
of 09/765,291 vs. 07/784,222
Grayetal. Westbrook
CON
09/765,291
IFW imaged
fd 1-22-01
DIV
10/608,092
IFW imaged
fd 6-30-03

DIETZ-BAND ET AL.

09/170,630
fd 10-13-98
PN 6,414,133

CLAIM SUMMARY DOCUMENT:

Claims 1-126 (Canceled).

Claim 127. (New) A DNA probe set, said probe set comprising a first probe set and a second probe set,

said first probe set being sufficient in length and substantially complementary to an entire breakpoint region of a first DNA and nucleotides on both sides of the breakpoint region but less than an entire chromosome such that said first probe set will hybridize to both sides of the breakpoint region regardless of whether the first DNA has been broken in the breakpoint region and either end fused to another DNA, and

said second probe set being sufficient in length and substantially complementary to an entire breakpoint region of a second DNA and nucleotides on both sides of the breakpoint region but less than an entire chromosome such that said second probe set will hybridize to both sides of the breakpoint region regardless of whether the second DNA has been broken in the breakpoint region and either end fused to another DNA.

Claim 128. (New) The probe set of claim 127, wherein said probes are detectably labeled.

Claim 129. (New) The probe set of claim 128, wherein said first DNA is part of the ABL1 gene on chromosome 9 and the second DNA is part of the BCR gene on chromosome 22.

Claim 130. (New) A diagnostic kit for detecting a structural abnormality caused by chromosomal breakage and rearrangement containing a reagent comprising at least one probe set of the probe set according to claim 127, and a container containing said reagent.

Claim 131. (New) A diagnostic kit according to claim 130 further comprising at least two containers, wherein a first container contains a reagent comprising said first probe set and a second container contains a reagent comprising said second probe set.

Claim 132. (New) A diagnostic kit according to claim 131 wherein said reagent comprises said first and said second probe set.

Claim 133. (New) A DNA probe set, said probe set comprising a first probe set and a second probe set,

said first probe set being sufficient in length and substantially complementary to an entire breakpoint region of a first DNA and nucleotides on both sides of the breakpoint region but less than an entire chromosome such that said first probe set will hybridize to both sides of the breakpoint region regardless of whether a second DNA from a region other than the breakpoint region has been inserted in the breakpoint region, and

said second probe set being sufficient in length and substantially complementary to a 3' end and a 5' end of a second DNA but less than an entire chromosome such that said second probe set will hybridize to both ends of the second DNA regardless of whether the second DNA is inserted in the first DNA.

Claim 134. (New) The probe set of claim 133, wherein said probes are detectably labeled.

Claim 135. (New) A DNA probe set, said probe set comprising a first probe set and a second probe set,

said first probe set being sufficient in length and substantially complementary to nucleotides on both sides of the breakpoint region of a first DNA but less than an entire chromosome such that said first probe set will hybridize to both sides of the breakpoint region regardless of whether the first DNA has been broken in the breakpoint region and either end fused to another DNA, and

said second probe set being sufficient in length and substantially complementary to nucleotides on both sides of the breakpoint region of a second DNA but less than an entire chromosome such that said second probe set will hybridize to both sides of the breakpoint region regardless of whether the second DNA has been broken in the breakpoint region and either end fused to another DNA.

Claim 136. (New) The probe set of claim 135, wherein said probes are detectably labeled.

Claim 137. (New) The probe set of claim 136, wherein said first DNA is part of the ABL1 gene on chromosome 9 and the second DNA is part of the BCR gene on chromosome 22.

Claim 138. (New) A diagnostic kit for detecting a structural abnormality caused by chromosomal breakage and rearrangement containing a reagent comprising at least one probe set of the probe set according to claim 135, and a container containing said reagent.

Claim 139. (New) A diagnostic kit according to claim 138 further comprising at least two containers, wherein a first container contains a reagent comprising said first probe set and a second container contains a reagent comprising said second probe set.

Claim 140. (New) A diagnostic kit according to claim 139 wherein said reagent comprises said first and said second probe sets.

Claim 141. (New) A diagnostic kit for detecting a structural abnormality caused by chromosomal breakage and rearrangement containing a reagent comprising at least one probe set of the probe set according to claim 133, and a container containing said reagent.

Claim 142. (New) A diagnostic kit according to claim 141 further comprising at least two containers, wherein a first container contains a reagent comprising said first probe set and a second container contains a reagent comprising said second probe set.

Claim 143. (New) A diagnostic kit according to claim 142 wherein said reagent comprises said first and said second probe sets.

US006414133B1

(12) **United States Patent**
Dietz-Band et al.

(10) **Patent No.: US 6,414,133 B1**
(45) **Date of Patent: Jul. 2, 2002**

(54) **MULTIPLE FUSION PROBES**

(75) Inventors: **Jeanne Dietz-Band**, Keedysville; **Wang-Ting Hsieh**, Bethesda; **John F. Connaughton**, Laytonsville, all of MD (US)

(73) Assignee: **Ventana Medical Systems, Inc.**, Tucson, AZ (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/170,630**

(22) Filed: **Oct. 13, 1998**

(51) **Int. Cl.**[7] **C07H 21/04**; C12Q 1/68; C12P 19/34

(52) **U.S. Cl.** **536/24.3**; 536/24.31; 536/24.32; 536/24.33; 536/23.1; 435/6; 435/91.1

(58) **Field of Search** 536/24.3, 25.3, 536/23.1, 24.31, 24.33, 24.32; 435/6, 91.1, 2, 91.2, 810

(56) **References Cited**

U.S. PATENT DOCUMENTS

4,999,290 A		3/1991	Lee	435/6
5,487,970 A	*	1/1996	Rowley et al.	435/6
5,538,869 A		7/1996	Sicilliano et al.	435/91.2
5,567,586 A	*	10/1996	Croce	435/6

OTHER PUBLICATIONS

TKachuk et al. Detection of BCR–ABL Fusion in Chronic Myelogeneous Leukemia by in situ Hybridization. Science. vol. 250, pp. 559–562, Nov. 1990.*

Fischer et al. Design and Validation of DNA Probe Sets for a Comprehensive Interphase Cytogenetic Analysis of Acute Myeloid Leukemia. Blood. vol. 88, pp. 3962–3971, Nov. 1996.*

Dewald et al, Blood, 91(9); pp. 3357–3365 (May 1, 1998).

Paskulin et al, Genes, Chromosomes & Cancer 21: 144–151 (1998).

Oncor 1992–1993 Product Catalog, p. 11 Oncor, Inc. 209 Perry Pky. Gaithersburg, MD.

1996/1997 Catalog, Vysis, Inc. 3100 Woodcreek Drive, Downers Grove, IL pp. 25 and 30.

TKachuk et al. Detection of BCR–ABL Fusion in Chronic Myelogeneous Leukemia by in situ Hybridization. Science. vol. 250, pp. 559–562, Oct. 1990.*

Dewald et al. Highly sensitive fluorescence in situ hybridization method to detect double BCR/ABL fusion and monitor response to therapy in chronic myeloid leukemia. Blood. vol. 91, No. 9, pp. 3357–3365, May 1998.*

Paskulin et al. Pre–Clinical Evaluation of Probes to detect t(8;21) AML minimal residual disease by fluorescence in situ hybridization. Genes, Chromosome and Cancer vol. 21, pp. 144–151, Feb. 1998.*

* cited by examiner

Primary Examiner—W. Gary Jones
Assistant Examiner—Cynthia Wilder
(74) *Attorney, Agent, or Firm*—Huw R. Jones; John E. Tarcza; Ann S. Hobbs

(57) **ABSTRACT**

The invention is directed to a DNA probe set, the probe set comprising a first probe set and a second probe set, the first probe set being sufficient in length and substantially complementary to an entire breakpoint region of a first DNA and nucleotides breakpoint region but less than an entire chromosome such that the first probe set will hybridize to both sides of the breakpoint region regardless of whether the first DNA has been broken in the breakpoint region and either end fused to another DNA, and the second probe set being sufficient in length and substantially complementary to an entire breakpoint region of a second DNA and nucleotides on both sides of the breakpoint region but less than an entire chromosome such that the second probe set will hybridize to both sides of the breakpoint region regardless of whether the second DNA has been broken in the breakpoint region and either end fused to another DNA. Diagnostic kits utilizing the probe sets of the invention are also claimed.

19 Claims, 10 Drawing Sheets

(1 of 10 Drawing Sheet(s) Filed in Color)

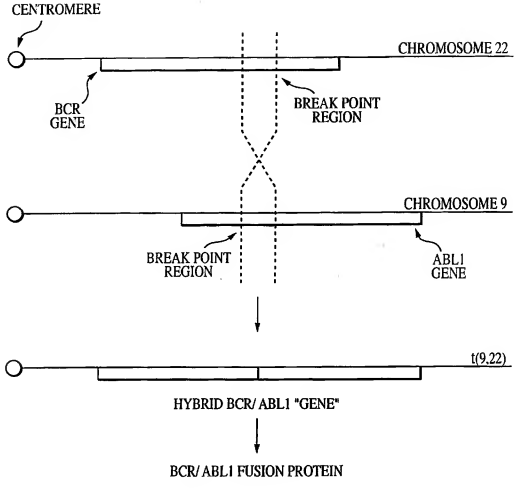

CENTROMERE
CHROMOSOME 22
BCR GENE
BREAK POINT REGION
CHROMOSOME 9
BREAK POINT REGION
ABL1 GENE
t(9,22)
HYBRID BCR/ ABL1 "GENE"
BCR/ ABL1 FUSION PROTEIN

FIG. 1

SCORING KEY:
R = RED SIGNAL = BCR
G = GREEN SIGNAL = ABL1
F = YELLOW SIGNAL BCR/ABL1 FUSION

FIG. 2a

SCORING KEY:
R = RED SIGNAL = BCR
G = GREEN SIGNAL = ABL1
F = YELLOW SIGNAL BCR/ABL1 FUSION

FIG. 2b

SCORING KEY:
R = RED SIGNAL = BCR
G = GREEN SIGNAL = ABL1
F = YELLOW SIGNAL BCR/ABL1 FUSION

FIG. 2c

SCORING KEY:
R = RED SIGNAL = BCR
G = GREEN SIGNAL = ABL1
F = YELLOW SIGNAL BCR/ABL1 FUSION

FIG. 2d

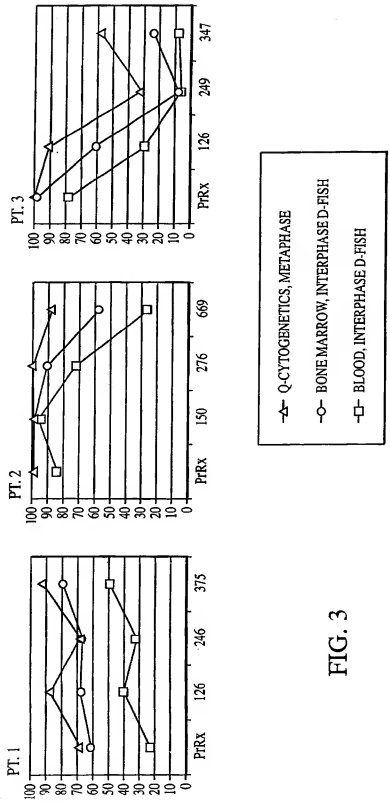

PT. 1
PT. 2
PT. 3
PrRx
0
10
20
30
40
50
60
70
80
90
100
126
246
375
150
276
669
249
347
Q-CYTOGENETICS, METAPHASE
BONE MARROW, INTERPHASE D-FISH
BLOOD, INTERPHASE D-FISH

FIG. 3

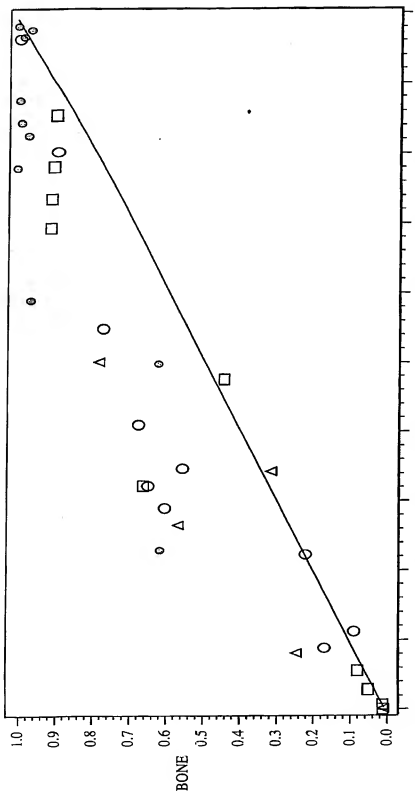


FIG. 4

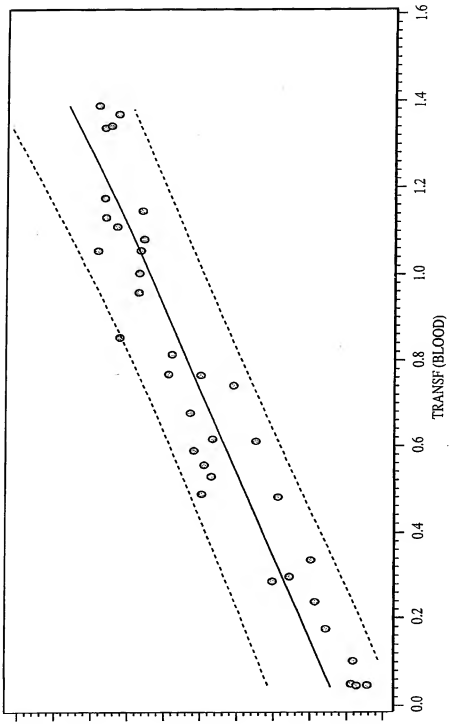

TRANSF BONE
1.90
1.70
1.50
1.30
1.10
0.90
0.70
0.50
0.30
0.10
-.10
0.0
0.2
0.4
0.6
0.8
1.0
1.2
1.4
1.6
TRANSF (BLOOD)

FIG. 5

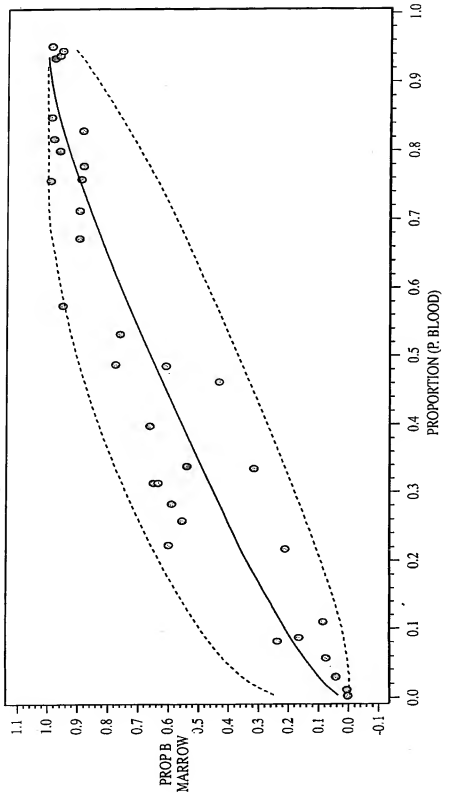

PROP B MARROW
1.1
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
-0.1
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
PROPORTION (P. BLOOD)

FIG. 6

TABLE 1: BCR SUMMARY

MAPPING OF BCR CLONES

BCR REGION CONTAINS 152,141 BP PUBLISHED SEQUENCE

NAME OF CLONE	CLONE TYPE	PRIMER PAIRS							CLONE SIZE (Kb)
		BCR26/27	BCR13/14	BCRA/B	BCRC/D	BCRE/F	BCR11/12	BCR17/18	
OCB 1004	PAC			+	+	+	+	+	214
OCB 1005	PAC				-	-	+	+	105
OCB 1001	PAC	+	+	-	-				154
OCB 1002	PAC	+	+	+	-				127
OCB 1003	PAC	+	-						147

+ : THE CLONE CONTAINS THE SEQUENCE AMPLIFIED BY THIS PRIMER SET.
- : THE CLONE DOES NOT CONTAIN THE SEQUENCE AMPLIFIED BY THIS PRIMER SET.

FIG. 7

TABLE 2: ABL SUMMARY

MAPPING OF ABL CLONES

3 SEQUENCES ARE AVAILABLE:

HSABLGR1, 35,692 BP, 5' ABL, EXON1B(29132-29267)/INTRON 1B(29268-35692)
HSABLGR2, 59,012 BP, PARTIAL INTRON 1B
HSABLGR3, 84,539 BP, INTRON 1B(1-37824)/EXON1A TO EXON10 AND POLYA

		PRIMER PAIRS								
NAME OF CLONE	CLONE TYPE	ABL5/6	ABL3/4	ABLa/b	ABLe/f	ABL9/10	ABLc/d	ABL7/8	ABL19/20	CLONE SIZE (Kb)
OC3002	P1	-	-	+	+	+	-			88
OCA1003	BAC	+	+	+	-					101
OCA1001	PAC	+	-	-		-				181
OCA1004	YAC				-	+	+	+	-	250
OCA1005	PAC						-	+	+	186
OCA1006	PAC						-	+	+	153
OCA1007	PAC						-	-	+	138

\+ : THE CLONE CONTAINS THE SEQUENCE AMPLIFIED BY THIS PRIMER SET.
\- : THE CLONE DOES NOT CONTAIN THE SEQUENCE AMPLIFIED BY THIS PRIMER SET.

FIG. 8

TABLE 3

		500 NUCLEI				6,000 NUCLEI				HYPERMETAPHASE
		BONE MARROW		PERIPHERAL BLOOD		BONE MARROW		PERIPHERAL BLOOD		BONE MARROW
			ABN		ABN		ABN		ABN	% ABN (PH POSITIVE/
PT	SPEC	%ABN	NUCLEI	%ABN	NUCLEI	%ABN	NUCLEI	%ABN	NUCLEI	METAPHASES ANALYZED)
4	3	0.6%	3	0.2%	1	0.22%	13	0.10%	6	0.0%(0/27)
4	4	0.4%	2	0.2%	1	0.23%	14	0.08%	5	0.0%(015)
4	5	0.0%	0	0.0%	0	NA	NA	0.13%	8	0.0%(1/169)
5	3	0.6%	3	1.0%	5	1.30%	78	0.95%	57	0.0%(0/136)
5	4	0.0%	0	0.2%	1	0.05%	3	0.12%	7	0.0%(0/126)
NORMAL CUTOFF		>0.8%	>4	>0.8%	>4	>0.079%	>4	>0.079%	>4	

FIG. 9

TABLE 4

		MEAN PROPORTIONS (+SE) ORIGINAL SCALE		ADJUSTED MEAN DELTA (+SE)
SAMPLE	PTS	BONE MARROW	BLOOD	(TRANSFORMED SCALE)
DX	10	0.91 (±0.05)	0.75 (±0.08)	0.165 (±0.047)
4 MOS	10	0.56 (±0.10)	0.41 (±0.09)	0.177 (±0.042)
8 MOS	10	0.49 (±0.13)	0.39 (±0.11)	0.150 (±0.042)
12 MOS	6	0.32 (±0.13)	0.20 (±0.08)	0.181 (±0.054)

FIG. 10

MULTIPLE FUSION PROBES

FIELD OF THE INVENTION

The invention relates to improved polynucleotide probe configurations for detecting structural abnormalities that result from chromosome breakage and rearrangement, particularly as used in the detection of several types of genetic disorders related to cancer and other diseases. The invention further relates to an improved method of detecting translocations using probe sets which span each breakpoint region associated with a translocation and the regions on both sides beyond the 3' and 5' ends of each breakpoint region.

BACKGROUND OF THE INVENTION

A number of inherited genetic diseases and types of cancer have been linked to chromosomal translocation events which result in the fusion of two genes which do not occur together in the normal genome. Certain conditions involve translocations which frequently occur at the same or very near location. The chromosome regions where frequent breaks occur are called breakpoint regions.

One of the best known examples of a clinically important translocation is the Philadelphia Chromosome which results from a break in the ABL1 gene on distal chromosome 9q and the BCR gene on proximal chromosome 22q {t(9;22)} (FIG. 1). The breakpoints within the ABL1 gene may occur throughout a region spanning more than 175 kb upstream from exon II while the breaks in chromosome 22 are clustered into two areas of the BCR gene, termed the major breakpoint cluster region (m-bcr) and the minor breakpoint cluster region (M-bcr) (Kurzrock et al, *New England Journal of Medicine*, 319:990 (1988)). The Philadelphia Chromosome occurs in most cases of Chronic Myelogenous Leukemia (CML) and some cases of Acute Lymphocytic Leukemia (ALL). Other important translocations include, but are not limited to, t(8;21) in Acute Myelogenous Leukemia, t(8:14) in Burkett's Lymphoma and pre-B-cell Acute Lymphoblastic Leukemia, t(1:14), t(7:9), t(7:19), t(11:14), t(10:14) and t(7:9) in T-acute Lymphoblastic Leukemia, t(15;17) in Acute Myelogenous Leukemia (AML) and t(15:17) Acute Promyelocytic Leukemia (PML). Solid tumors include, t(9;22) in Ewing's Sarcoma, t(15:16), and hereditary diseases associated with translocations include a number of mental retardation associated syndromes. It is likely that other conditions are caused by subcriptic translocations or other structural aberrations which are yet to be determined and are too small to be noticed by standard cytogenetics.

Multiple genetic testing methods have been developed for use in diagnosis, monitoring of minimal residual disease and/or response to therapy during clinical practice. However, no single technique has been developed that can accurately detect and quantify disease at diagnosis and throughout treatment. Conventional quantitative cytogenetics and G-banding analysis is cumbersome and can only be applied to cycling cells (Lion, Leukemia 10: 896 (1996)). In practice, the sensitivity of conventional cytogenetics is dependent upon the number of good metaphase cells which can be evaluated. In the example of cancers caused by neoplastic cells in the bone marrow, obtaining large numbers of good metaphase cells from bone marrows of patients is difficult.

More recently, the assay technique in situ hybridization (ISH), particularly fluorescent in situ hybridization (FISH) (Pinkel et al, *Proc. Natl. Acad. Sci., U.S.A.* 83:2934–2938 (1986)) has been of assistance in detecting translocations.

FISH allows the analysis of individual metaphase or interphase cells, thereby eliminating the need to obtain and assay cycling cells. It is therefore possible to use nondividing tissue, including bone marrow and peripheral blood cells in a diagnostic or prognostic analysis.

In the field of detecting the Philadelphia Chromosome, a commonly used method for detection of ABL1/BCR fusion utilizes differently labeled probes for BCR and ABL1, and detects a single ABL1/BCR fusion (or closely linked) signal in cells with a Ph chromosome. (This method is referred to for convenience as S-FISH.) An example of this technique is Tkachuk et al, *Science* 250: p. 559–562 (1990) where one fluorescently labeled probe hybridized to part of the ABL1 gene and a second fluorescently labeled probe hybridized to part of the BCR gene.

The probes in commercial single FISH test kits do not span the entire length of each translocation breakpoint but rather are designed to bind to one portion of each gene, i.e. sometimes overlapping or adjacent to a breakpoint region, sometimes many kilobases away and sometimes both (See FIG. 1 of Tkachuk et al for example). Normal chromosomes 9 and 22 each bind one probe, which is specific to that chromosome. The Philadelphia Chromosome, both probes hybridize at the fusion site bringing both labels in close proximity so as to usually form a color shift or fusion near proximity/signal. Because the exact breakpoint may vary, the two probe labels may not come sufficiently close to form a fusion label. Likewise for probes useable to detect the t(8:21) translocation in Acute Myelogenous Leukemia (AML).

Using the probe configuration above, the following detection method for the Philadelphia Chromosome using FISH has been used: the ABL1 gene probe is labeled using a probe containing one hapten or fluorophore (for example, FITC) and the BCR gene probe is labeled using a probe containing another hapten or fluorophore (for example Rhodamine). After hybridization and detection, a normal chromosome 9 shows the green signal and a normal chromosome 22 shows a red signal. A normal cell would therefore exhibit two red signals and two green signals. A cell containing a Philadelphia chromosome has one red and one green signal for the unaffected homologues of chromosomes 9 and 22 and one white, yellow or closely linked pair of signals that results from the close proximity of the labeled probes hybridized to the translocated BCR and ABL1 genes, the so-called fusion signal.

However, the probes used heretofore in this method have not been constructed so as to specifically bind and detect the second fusion site for the reciprocal translocation event. Thus, the S-FISH method detects only one of the abnormal chromosomes resulting from the translocation event, the Philadelphia chromosome.

In another method using labelled probes to detect ALL gene rearrangements in solid tumors, a probe set was designed so that the two probes lie adjacent to each other on the normal chromosome, but split apart and move to the two different abnormal chromosomes if the translocation has occurred (Croce, U.S. Pat. No. 5,567,586, hereby incorporated by reference). In this method the probes are designed to be complementary to sequences in the translocation region on one chromosome. In this method, the fluorescent probes produce a single spot on the normal chromosome, but appear as two distinct spots when translocation has occurred.

The same format has been used for other assays for detecting other translocations such as t(8:21) in Acute

Myeloid Leukemia (AML). For example, Le Beau, Blood 81: 1979–1983 (1993), and Sacchi et al, Cancer Genetics and Cytogenetics 79: 97–103 (1995) and Fischer et al, Blood 88: 3962–3971 (1996).

SUMMARY OF THE INVENTION

It is an object of the invention to provide methods with increased sensitivity and accuracy for detecting chromosome translocations and other structural rearrangements which result in more than one abnormal fusion site in the genome.

It is a further object of the invention to provide probes and probe sets which are useful in detecting reciprocal genetic translocations according to the methods of the invention.

It is another object of the present invention to detect cancer, inherited disease, susceptibility to inherited disease or a carrier of a fused gene for an inherited disease wherein the condition results from a chromosomal translocation in one or more cells. This is particularly beneficial when the diagnosis, prognosis, monitoring for residual disease and response to therapy in cancer or other disease is dependant upon the quantity of abnormal cells as an indicia of the disease state and/or response to treatment.

It is also an object of the invention to provide a means of constructing such probes and probe sets, which will detect reciprocal fusions resulting from chromosomal translocations and will accordingly be useful in diagnosis, prognosis, monitoring of residual disease and response to therapy when reciprocal chromosome translocations are present.

It is still another object of the present invention to provide diagnostic test kits which can be used by any cytogenetist or other trained individual to detect multiple fusion events which result from structural rearrangement of the genome.

Probes and probe sets of the present invention have the characteristic of encompassing the entire breakpoint region and a region on each side of the breakpoint region on each chromosome for the reciprocal translocation event of interest and are capable of detecting such translocations with much greater sensitivity than the probes and probe sets which were previously known.

A particularly preferred probe set and method is used for detecting the Philadelphia chromosome and its corresponding derivative chromosome as companion indicators of CML and some other cancers such as ALL. One functional probe is designated P5161-DC, described hereinbelow. Another example is for detecting the AML1/ETO gene fusion in AML.

The use of specifically designed probe sets by the method of the present invention has allowed the clinician to assess physical information regarding all fusion events associated with a defined structural rearrangement in a cell. For example, using the standard detection method of fluorescence in situ hybridization (FISH) it has been demonstrated that these probe sets provide the following advantages over traditional testing methodologies for detecting the same translocation.

1. Unlike traditional single fusion probe sets, probe sets which detect multiple, derivatives of a structural rearrangement have the ability to detect much lower copy numbers of abnormal cells thereby providing greater improved diagnostics using FISH assays
2. The ability of the probe sets to derive necessary information from cells in interphase, Thereby rivaling the sensitivity of metaphase cells in conventional cytogenetics.
3. Specifically, increased sensitivity has been demonstrated with multiple fusion probes used in interphase FISH analysis which is at least as sensitive as Q-cytogenetics (the previous gold standard) for monitoring bone marrow or peripheral blood cell populations for minimal residual disease and response to therapy.
4. Greater sensitivity allows the use of peripheral blood instead of invasive and painful bone marrow samples from patients for routine testing, to monitor for minimal residual disease and response to therapy.
5. By detecting high and low copy numbers of gene fusions, the present invention can be used for diagnosis and monitoring throughout the course of the disease thereby avoiding traditional multiple assay-type testing methodologies.
6. Simplified sample requirements and testing provides further benefits in cost and patient well being.

BRIEF DESCRIPTION OF THE DRAWINGS

The file of this patent contains at least one drawing executed in color. Copies of this patent with color drawing will be provided by the Patent and Trademark Office upon request and payment of the necessary fee.

FIG. 1 shows a schematic drawing of a BCR/ABL1 translocation and probes constructed according to the invention.

FIG. 2A shows the appearance of a normal cell after testing with probe P5161-DC using the methods of the invention. The two red signals designate the BCR genes on chromosome 22 and the two green signals designate the ABL1 genes on chromosome 9.

FIG. 2B shows the appearance of a cell containing a BCR/ABL1 translocation after testing with probe P5161-DC using the methods of the invention. One red, one green and two fused signals denoting both of the reciprocal translocation events are present.

FIG. 2C also shows the appearance of a cell containing a BCR/ABL1 translocation after testing with probe P5161-DC using the methods of the invention. Two red, two green and one fused signals are present in this example. While two fusion signals are usually detected, because of the physical configuration of the gene and the relaxation of the heterochromatin in interphase, a red and a green signal may appear to be closely linked but not quite overlapping. Note the two signals at the lower end of the field which are not quite fused. This configuration is believed to represent the fused portion of a translocation event.

FIG. 2D shows the appearance of a cell containing a BCR/ABL1 translocation after testing with probe P5161-DC using the methods of the invention. One red, one green and three fused signals are present. This cell contains an additional Philadelphia chromosome.

FIG. 3. Percentage of Ph positive cells (Y-axis) prior to therapy and during treatment at approximately 4 month sampling intervals (X-axis in days) in bone marrow by Q-cytogenetics and D-FISH, and blood by D-FISH.

FIG. 4. Relationship between the percentage of Ph positive cells for paired-sets of bone marrow (Y-axis) and peripheral blood (X-axis).

FIG. 5. Linear regression analysis of the (transformed) proportion of abnormal cells from bone marrow on the (transformed) proportion from peripheral blood from FIG. 4. Dashed lines are the 95% prediction interval.

FIG. 6. Results of linear regression analysis but transformed to original scale of proportions of abnormal cells for bone narrow (Y-axis) versus peripheral blood (X-axis). Dashed lines represent the 95 prediction internal for a bone narrow prediction given a specific peripheral blood score.

FIG. 7. BCR map and summary of probe listed as Table 1.

FIG. 8. ABL1 map and summary of probe listed as Table 2.

FIG. 9. Data and comparison of different techniques for assaying for the Philadelphia chromosome, listed as Table 3.

FIG. 10. Data comparing bone marrow and blood samples for monitoring the disease state and response to therapy, listed as Table 4.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is an assay and reagents therefore which may be packaged into a simple test kit. The reagent comprises two probes, the first complementary to and encompassing the entire breakpoint region on a first chromosome as well as both upstream and downstream regions from the breakpoint region. As such, the first probe will hybridize to a normal first chromosome as well as both fragments of the first chromosome which have undergone a translocation or break and may be rearranged elsewhere. The second probe is the same as the first except for spanning the entire breakpoint region, as well as both upstream and downstream regions on the second chromosome. Kits may also be constructed for multiple translocation events or having more than two chromosomes involved according to the methods of the present invention.

Each probe is detectable when hybridized to the target DNA, preferably by being labeled with a unique detectable label that can be either directly or indirectly detected. The labeling may be by covalent bonding or other affinity attachment. Each polynucleotide comprising a probe is labeled with the same label and each probe has a detectably different label from other probes in the mixture. As such, one can easily detect each normal chromosome potentially involved in the translocation as well as fusions between the two or more breakpoint regions which are detected as a fusion signal.

The different construction of multiple fusion probes provides numerous advantages over two similarly labeled single fusion probes hybridizing to different locations. Some of these advantages were not apparent until after testing the probes on biological samples. Thus, by constructing probes complementary to the entire breakpoint regions, as in D-FISH, one achieves certain advantages over conventional S-FISH.

In the present invention's improved method, designated D-FISH, fusion signals can be detected in each cell as an indicator of the presence of a reciprocal translocation. The sensitivity of the method using the available S-FISH probes has not been sufficient in the past to detect very low levels of translocations which are found in the peripheral blood cells or bone marrows of many patients. Specifically, commercially available S-FISH detects about 70–75% of patients actually positive for the Philadelphia chromosome. Actual positive results were necessarily determined by sequencing, PCR amplification or Southern blotting. By contrast, using D-FISH with the probes of the present invention detects greater than 99% of patients actually positive. This data rivals or exceeds standard Q-cytogenetics (See Dewald et al data). The improved detection indicates that the present invention should be accepted as the "gold standard" by which all other assays are compared.

This improved sensitivity is accomplished by using probes which are specifically developed to cover the entire breakpoint region of each chromosome involved in the translocation. In such a translocation, the labeled probe for a first chromosome is immediately adjacent to the labeled probe for a second chromosome thereby producing multiple fusion signals. By contrast, S-FISH employs probes which are designed to be complementary to one side of each of two breakpoint regions and therefore relies upon the detection of a single fusion event.

The new method presented here involves novel DNA probe constructs which are designed to target the length of each breakpoint region in a translocation event and additional DNA sequence beyond both the 3' and the 5' ends of each breakpoint region. When the breakpoint region occurs in a gene, it is preferable for the probes to encompass the entire gene and additional DNA sequence beyond both ends also. When used together, all reciprocal translocation events involving the target gene regions can be detected simultaneously in an interphase or metaphase cell. The probes are further designed to give easily visualized balanced signals in interphase cells.

The effectiveness of dual or multi-fusion probes is perhaps best demonstrated when the DNA probes are fluorescently labeled in different colors and hybridized to cellular DNA using the standard assay technique of fluorescence in situ hybridization (FISH) (Pinkel et al, *Proc. Natl. Acad. Sci., U.S.A.* 83:2934–2938 (1986)). Various types of DNA probe configurations have been used with FISH technology in an attempt to find a reliable and sensitive assay for interphase cell analysis. However all of these techniques provide either too many false positives, false negatives or simply lack the sensitivity to determine the presence of the translocation in interphase detection of minimal residual disease and/or response to therapy. Additionally, other techniques are cumbersome or expensive to test or require large quantities of hard-to-obtain biological material. By comparison, the Examples below show obtaining a result from a simple blood sample using conventional cytogenetic equipment with a high sensitivity and low error rate.

Balanced and non-reciprocal translocations may also be detected using the probe strategy and method of the present invention. Even inversions within the same chromosome may be detected as double fusions with the probe sets developed for the two breakpoint regions on the same chromosome. In such situations, one still has two breakpoint regions forming at least one fusion site for detection of a fusion signal. The same general principles apply either way. In accordance with the present invention, probes constructed in accordance with the general instructions provided herein are used to produce reagents and a method for detecting multiple breaks as well as any resulting fusions thereby determining the presence of such multiple breakage events simultaneously. The present invention may also be used for screening for chromosome breakage at multiple genome sites due to environmental factors, chemicals, radiation (diagnostic X-rays or radiation therapy or radiation exposure), biological agents etc.

The source of cells may be highly variable. If a cancer is being diagnosed or monitored, cells from the tumor site or removed from the tumor site may be used. For inherited diseases, readily available cells from tissues, blood, urine, feces, buccal scrapings, cervical and vaginal scrapings (PAP smear), body fluids, etc. may be used. For prenatal testing, fetal, amniotic, placental, cord, chorionic villus, and "cells" including sperm or egg for the situations of gamete "donation" or in vitro fertilization may be used.

The cells being tested may be in any phase, but metaphase and interphase are preferred.

While this application generally refers to humans and human diseases, persons of skill will appreciate the invention is useful in other settings. The present invention is equally applicable to other animals for agricultural or veterinary purposes as useful in the diagnosis, prognosis and monitoring of disease. If so desired, the present invention is applicable to determining translocations in plants as well. The present invention is also applicable to non-disease conditions where determining the presence of a translocation is important for plant and animal breeding such as to follow the presence of a trait throughout generations.

One standard method for plant breeding involves infecting the plant with Agrobacterium tumefaciens carrying a Ti plasmid which will integrate T-DNA into the plant chromosome. Transfection of the plasmid per se may also be used. A desired gene is typically incorporated into the T-DNA region, especially in a hormone gene if not already deleted. In such a situation, the plant chromosome has a breakpoint region for inserted T-DNA. Probes encompassing the plant chromosome breakpoint region and the two ends of the T-DNA or the desired gene may be used to determine whether plant cells contain the desired gene. The present invention results in considerable time savings compared to tissue culture and cultivation of the plant to maturity and testing for a trait caused by the desired gene.

Along the same procedural lines, the present invention may be used to assay for insertion of any other DNA into a specific chromosome site such as is desirable in gene therapy. During certain forms of gene therapy, added DNA is incorporated into the host chromosomes at specific locations. The present invention permits monitoring and provides proof of integration.

Viruses which integrate are biologically significantly different when their DNA is integrated into a host chromosome. Such an integration involves a breakage of the chromosome and a fusion of the viral DNA into the chromosome. Monitoring the integration is an important step in assaying for antiviral therapeutics, determining prognosis, etc. If the integration site or region is known, probes to that site and to the virus (or viruses if two are coinfecting) may be prepared and used according to the present invention.

False positives can occur in normal cells, for example when the BCR locus of chromosome 22 coincidently occurs very close to, behind or in front of the ABL1 locus of chromosome 9. Since the cell being viewed is three dimensional and usually in interphase, the chromosomes are freely moving within the cell nucleus permitting a random juxtaposition of signal. About 4% of normal slides have the two loci sufficiently superimposed on each other to cause the signals to appear fused using S-FISH.

However, when using D-FISH, two fusion signals typically occur as well as two normal signals. The percentage of normal cells with both ABL1 and both BCR loci coincidently superimposed is very small. Thus, the false positive rate in D-FISH is lower. Still further, normal cells displaying two fusion signals by chance would not display two normal signals as well, providing a further check against false positives.

As for reducing the false negative rate and increasing sensitivity, one potentially has twice as many fusion signals per cell which makes it easier to detect an abnormal cell.

The advantages of the present invention depends upon a number of factors, including the unique probe configuration, the number or percentage of affected cells, which may vary with individuals and disease states. For example, the methods described above typically require that about 1% of the cells be affected for accurate signal detection. This compares to a S-FISH assay requiring about 30% of the cells positive. If fewer cells are affected, an abnormal condition may not be detected.

While the Examples use microscopic identification of normal and abnormal chromosomes, other techniques may be used. For example, cells may be observed and determined to contain or not contain a translocation during flow cytometry or extracts may be taken and conventional DNA hybridization assays performed.

Several factors determine how large a probe construct should be. In the example of the BCR gene, for example, the probe would be sufficiently long to include both the major breakpoint cluster region and the minor breakpoint cluster region, as well as sequences beyond the gene. For other genes exemplified below, the breakpoint region is widely variable in size and requires probes of sufficient size unique to each application and may be determined by routine optimization. Generally, the probes will have a considerable length complementary to the adjacent non-breakpoint region for a normal or translocated fusion configuration. The length will depend on the particular translocation being detected. The length of each probe will further be manipulated to make visually balanced signals and/or enough to routinely cause a color shift when the signal is fused to a different label's signal. The length must accommodate all breaks, regardless of where in the breakpoint region the actual breakage and fusion occurs. Preferably, the length is also be sufficient to provide fusion signals of similar size throughout the target clinical population of cells, thereby increasing reliability and ease of interpretation.

Generally, the length of the probe sets will correlate to the length of the largest breakpoint region involved in a translocation event. Thereby, the balance of fusion signals in interphase cells is assured. The length may also be affected by the amount of label which can be incorporated on the probe. Considerable variance is acceptable, if there is optimization of labeling conditions for each probe being developed.

In one preferred embodiment of the invention, one probe of a probe pair is designed to be complementary to the ABL1 sequence (600 Kb) and the other probe is designed to be complementary to the BCR sequence (500 Kb). Individual cloned human DNA probes of varying lengths complementary to the ABL1 and BCR breakpoint regions were used collectively to make probes of appropriate length. A single clone may be used; however, if the insert is of sufficient size. In practice, probes are developed from overlapping "probe sets", consisting of several cloned DNA sequences which hybridize to and span the breakpoints on the relevant chromosomes.

Alternative techniques may be used other than FISH for probes of the present invention. For example, during the use of conventional blot assays, Southern and Northern, probes of the present invention may be optimized to be used in lieu of other labeling techniques. The probes of the present invention may also be used in developing assays in aqueous solution.

The probes of the invention may be detected after it is hybridized to the target DNA or RNA. This may be done by any technique which detects a probe containing double stranded DNA within the biological sample. If the remainder of the sample lacks significant double stranded regions, one may use chemicals which specifically bind to double stranded but not single stranded DNA or DNA/RNA. Examples include a labeled antibody to double stranded

DNA or RNA/DNA followed by detecting the label, ethidium bromide, SYBR green, an acridine dye (e.g. acridine orange), a protein or enzyme, etc.

The more preferred option is to have the probes labeled in order to provide a means of detection. Suitable labels include, but are not limited to, haptens and fluorophores, such as, FITC, Rhodamine and Texas Red as well as radioactive, chemiluminescent, bioluminescent, a metal chelator, quencher, enzyme, chemical modifications rendering the DNA detectable immunochemically or by affinity reactions, and other known labels. Many such suitable detection labels are known to persons of skill in the art of binding assays such as nucleic acid hybridization assays and immunoassays. When the label is a hapten, a receptor labeled directly or indirectly with an easily detectable substance, is employed before, with or after hybridization of the hapten labeled probe. When the label is a quencher, the absence of or reduced signal indicates the presence of the quencher.

Common ways to incorporate the label into the probe include nick translation, random priming or PCR amplification using a derivitized dNTP or NTP. Also post probe synthesis labeling and end labeling may be performed. The amount of label varies from one probe to another and the various uses for the probes. Too much labeling may actually cause a quenching effect. Typically about 1–25% of a nucleotide (A, G, C, or T) will be modified to incorporate a label into a DNA probe.

One of ordinary skill can choose appropriate labeling techniques, other colors or detection strategies which may vary depending on the particular translocation or other fusions being detected.

DEFINITIONS

As used herein, the term "probe" is intended to mean one or more polynucleic acids which hybridize specifically to a particular region of chromosome which is of interest. Depending on the size of the region, multiple polynucleotide molecules may be combined to comprise the probe. The number of polynucleotides will also be determined by whether the polynucleotides are synthesized chemically, by PCR, by plasmid, by cosmid, by yeast artificial chromosome (YAC) etc. Individual molecules comprising the probe may hybridize to overlapping portions of the chromosome of interest or may hybridize to physically linked regions separated from each other. These gaps may be sizable but should not be so large that upon hybridizing to a translocation locus in a cell, the probes are so far apart that they appear as non-associated signals and no fusion event can be reliably detected. For example, a 100 base pair gap is probably insignificant whereas a 1 Mb gap is too much to be acceptable. Note that the break may occur anywhere in the breakpoint region and therefore construction of the polynucleotide molecules composing the probe should be designed to accommodate breaks at the worst possible locations.

A probe need not have exact complementarity to the desired target, but should have sufficient complementarity to bind to the region of interest using the methods of the invention. To achieve this generally requires a matching sequence with at least 80%, preferably 95%, and most preferably about 100% complementarity to the target. Occasional polymorphisms may preclude true 100% complementarity in some individuals, particularly when the breakpoint does not occur in a coding sequence.

Accordingly, as used to refer to probes herein, the term "complementary" includes "substantially complementary" which is intended to refer to a probe which will specifically bind to the region of interest on a chromosome under the test conditions which are employed, and thus be useful for detecting and localizing the region. Complementarity will be extensive enough so that the probes will form specific and stable hybrids with the target DNA under the hybridization conditions used. Persons of skill in the art will be able to determine suitable sequences through the general knowledge available in the art, and by routine experimentation, using the examples set forth hereinbelow as guidelines.

A "cell" as used herein includes biological samples which were derived from cells. "Biological sample" includes all nucleic acid containing compositions where the nucleic acid (RNA or DNA, chromosome, viral, vector, mitochondrial . . .) was obtained from an individual organism or amplified from a nucleic acid obtained from an individual organism. The slide preparation procedure used in the Examples actually kills the cell and removes some of its components. However, the DNA remains. The term "cell" as used herein includes cellular components, extracts and other partial cellular components provided that they contain the nucleic acids. It is preferred that a reasonably complete set of the chromosomes remains or at least the DNA of the breakpoint regions and adjacent regions remains such that one can determine normal untranslocated DNA sequences from fused DNA sequences resulting from a translocation.

A "translocation" is the exchange of genetic material between two or more non-homologous chromosomes. This is frequently a reciprocal event where two chromosomes are simultaneously broken and the fragments are exchanged between the two chromosomes. Two new chromosome derivatives are created.

A piece of a chromosome may be broken twice and reincorporated in the same region in reversed order. This is called a inversion and is a subset of structural abnormalities caused by chromosomal breakage and rearrangement.

The present invention has many uses other than detecting reciprocal translocations such as detecting other chromosomal abnormalities caused by chromosomal breakage and rearrangement such as insertions, inversions, derivative chromosomes and possibly duplications and ring formations.

As used herein, the phrase "the entire breakpoint region" is intended to refer to a sequence or probe of sufficient length to include the entire region in which a particular break may occur. This region will vary with the particular structural aberration one wishes to detect. In rare instances where the boundaries of the breakpoint region may not be completely known or unclear, the breakpoint region is the region encompassing the distribution of two standard deviations of known breakpoints.

A "contig" is a collection of two or more overlapping cloned DNA fragments that when used together will extend the target region beyond that of using a singular cloned fragment. A contig refers to "contiguous" DNA fragments.

EXAMPLE 1: CONSTRUCTION OF BCR/ABL1 DUAL FUSION PROBES

The BCR/ABL1 dual fusion probes were assembled by screening through several different human libraries cloned into PAC, P1, BAC, and YAC vectors available from commercial sources, e.g. a CEPH library. The procedure included several rounds of sequencing and walking. These methods are known to persons of skill in the art and are described in various molecular procedure manuals such as PCR Protocols, A Guide to Methods and Applications, Innis et al, Academic Press, Inc. (1990) incorporated herein by reference.

Each round of screening included the following steps:

1. Synthesizing new PCR primers based on sequence information.
2. Establishing PCR conditions for the new primers.
3. Screening the libraries by either PCR (using primers) or DNA hybridization (by amplified fragments).
4. Selecting the positive clones.
5. Evaluating the positive clones by FISH. Verifying that the positive clone hybridizes to the correct region and does not show any cross hybridization.
6. Obtaining the end sequences of the insert of new clones by either direct sequencing or by sequencing the purified end fragment amplified by using a combination of Alu or other primers and vector end primers.
7. Comparing the new sequence to the existing sequence to establish the relative location of the new clone. New primers were then made from the new sequence outside the existing sequence.
8. Repeating steps 2–7 until the probes reached the appropriate length to include the entire breakpoint region and achieve the desired FISH signal intensity.
9. Establishing the relative locations of all clones in the final contig by STS mapping and estimating the size of the contig.

To obtain multiple fusion probes according to the invention, it is preferred that the probes cover both sides of the breakpoint and show not only good but also balanced signals in affected cells. For both BCR and ABL1 probes, screening was done for clones which collectively hybridize to the entire breakpoint region and both sides of the breakpoint region containing normal chromosomal DNA.

BCR:

The BCR dual fusion probe set is composed of 5 human PAC clones which are shown in Table 1, FIG. 7.

The BCR region contains a 152141 bp sequence published by GenBank. Three primer pairs were initially made, BCR a/b, BCR c/d, and BCR e/f, which correspond to the gene sequence at the −15 kb, −123 kb and −152 kb, 5' to 3' positions respectively. These primer sets were used to screen a P1 library by PCR and the amplified fragments were isolated and pooled to screen a PAC library by hybridization. Several positive P1 and PAC clones containing BCR gene sequences were obtained.

P1 Clone OC2001 was scored positive using primers BCR a/b. The end sequences of the insert were obtained. This clone has one end of the insert located in the BCR known sequence and one end outside the 5' end of known sequence. Primer set BCR 13/14 was synthesized using the new sequence information. Both PAC OCB1001 and OCB1002 were obtained by screening using BCR 13/14. The next round of screening was done by first sequencing the end sequences of the insert in PAC OCB1001, establishing the 5' and 3' positions of the ends and primers BCR 26/27 were made. PAC OCB1003 was acquired by screening the PAC library using the new primers BCR 26/27. This PAC is on the most 5' end of the contig.

PAC OCB1004 was obtained from the hybridization of PAC library using the pooled amplified DNA fragments generated by the BCR a-f primers described above. This clone covers almost all the BCR known sequence and also extends in the 3' direction.

From the PCR screening of the P1 library using primers BCR e/f, P1 clone OC2002 was obtained on the 3' end of the gene. Both ends of the insert were sequenced. This clone contains the BCR gene sequences from the 3' position, 109 kb into the gene, and extends further in the 3' direction from the end of the BCR gene. A new primer pair BCR 13/14 was made using the new 3' end sequence. PAC OCB1005 was obtained from the new screening which became the furthest 3' clone in the contig.

The size of the inserts of these individual clones are estimated by adding up all the EcoR1 restriction fragments found on agarose gel as compared to commercially available molecular weight DNA markers. The relative locations of all the clones are established by whether the clones are positive or negative to all the PCR primer sets tested. Because the entirety of the clones were not sequenced, the extent of overlap or gaps (if any) present in the clones has not been characterized. However, the clones are known to contain sequences in common to other clones within the BCR probe set. The total size of the BCR contig is approximately 500 kb.

ABL1

The ABL1 dual fusion probe set consists of 1 BAC, 1 P1, 4 PAC and 1 YAC clone as shown in Table 2, (FIG. 8).

The ABL1 region contains 3 segments of published GenBank sequences: HSALBGR1, 35,692 bp, covering the 5'ABL1 exon 1b and part of intron 1b, HSABLGR2, 59,012 bp containing portions of intron 1b and HSABLGR3, 84,539 bp extending from the end of intron 1b to the end of exon 10 and poly A region. The intron 1b is about 200 kb in length.

The initial screening was done in a similar way to screening for five BCR probes. Three primer sets were synthesized, ABL1 a/b, ABL1 c/d, and ABL1 e/f. ABL1 a/b is located >2000 bp in from the 5' end of the HSALBGR1 sequence, see table 2, FIG. 8. ABL1 c/d is ~79,000 bp in from the 5' end of the HSABLGR3 sequence, and ABL1 e/f is located ~31,000 bp in from the 5' end of HSABLGR2 sequence. The ABL1 a-f primers were used to screen a P1 library directly by PCR and the amplified fragments from these primers were used to screen a PAC library by DNA hybridization. Several positive P1 and PAC clones were identified.

The P1 clone OC3001 was obtained from PCR screening using primers ABL1 a/b. The clone covers a small segment of the HSABLGR1 sequence and extends further in the 5' end of ABL1. A new primer set ABL1 5/6 was made after sequencing the end of the OC3001 insert. ABL1 5/6 was used to screen a PAC library and the PAC clone OCA1001 was acquired. The OCA1001 clone contains the most 5' end of the contig. The P1 clone OC3002 was obtained by PCR screening using primers ABL1 e/f. This clone contains most of the HSABLGR1 and HSABLGR2 sequence regions.

PAC clone OCA1002 was obtained by hybridization screening using the pooled amplified fragments generated by the ABL 1 a-f primers. This PAC clone also extends outside the 5' end of ABL1 gene. The end fragments of the insert were sequenced and primer set ABL1 3/4 was made. ABL1 3/4 was used to screen a BAC library. The BAC clone OCA1003 was identified.

YAC clone OCA1004 was obtained from the commercially available library. OCA1004 contains a portion of HSABLGR2 sequence and extends beyond the 3' end of the HSABLGR3 region. The end fragments of OCA1004 were isolated and sequenced. Primer pair ABL1 7/8 was made and used to screen a PAC library. PAC clone OCA1005 was obtained. A new primer set, ABL1 19/20, was synthesized using sequence information obtained from clone OCA1005. Both PAC OCA1006 and OCA1007 were identified by library screening using ABL1 19/20.

The sizes of the inserts of the clones in the ABL1 probe set, except for the YAC, were estimated by summing up EcoR1 restriction fragments visualized on an agarose gel. The size of YAC clone was determined by comparing to

known size standards on a gel. The relative positions of all the clones were determined from using the primer sets developed for screening DNA bands as physical map anchor sites throughout the ABL1 region. The total length of this contig is approximately 600 kb.

The combination of the BCR and ABL1 probe sets described above defines a dual fusion probe set for t(9;22). It has been designated P5161-DC. The skilled artisan will appreciate that by using these and other techniques known in the art, additional suitable probe sets would be constructed for the ABL1/BCR translocation and for other translocations of interest.

EXAMPLE 2: USING THE PROBE SET FOR CML D-FISH ASSAYS

The P5161-DC probe set was used in standard FISH protocols to devaluate the usefulness of using dual fusion probes (D-FISH) FOR DETECTION. The study of Philadelphia chromosome in a CML clinical population included 37 paired-sets of bone marrow and peripheral blood specimens from 10 patients undergoing treatment for CML, 10 normal peripheral blood specimens, 10 normal bone marrow specimens and four serial dilutions with known percentages of Ph positive nuclei.

Each patient with CML was a participant of the CML National Study Group clinical trial and was randomly receiving treatment with interferon α-2b with or without ara-C. Each patient was known to have cells with a Ph chromosome that produced a typical D-FISH pattern (two fusion signals, two normal signals) for t(9;22)(q34;q11.2). For each patient a paired-set of bone marrow and peripheral blood specimens were collected prior to treatment and at two or more times at approximately 4-month intervals during treatment. Each paired-set of peripheral blood and bone marrow specimens was obtained on the same day except for specimens collected prior to treatment in patients 3 (blood and bone marrow were collected 1 day apart), 5 and 8 (blood and bone marrow were collected 4 days apart).

Uncultured bone marrow and peripheral blood specimens were processed by conventional procedures for cytogenetic and FISH studies. These specimens were stored as fixed pellets at −70° C. in methanol:acetic acid (3:1) until FISH studies could be performed. The D-FISH specimens were prepared by being washed twice with fresh fixative and cells were placed on microscope slides and allowed to air-dry in a CDS-5 cytogenetic drying chamber (Thermotron, Holland, Mich.) adjusted to 50% relative humidity and 25° C. Slides were further dried for 1 hr in a 65° C. oven and then treated with 2× standard saline citrate solution (SSC) (300 mmol/L sodium chloride, 30 mmol/L sodium citrate) for 1 hr at 37° C. Slides were then dehydrated with 70–85–100% cold ethanol (stored at −20° C.) for 2 minutes each, and air-dried.

The FISH hybridization and detection procedure was carried out as follows. Chromosomal DNA (in the form of cells on a slide) was denatured in 70% formamide/2×SSC for 2 min at 70° C. Slides were dehydrated with an ethanol series (70%, 85% and 100%) for 2 min each and air-dried. The probe (Oncor product #P5161-DC) was denatured in a water bath at 70° C. for 5 min. Then 10 μl of stock solution BCR/ABL1 probes were added to each slide, a 22×22 mm coverslip placed on the slide and sealed with rubber cement. Slides were hybridized for 18–20 hrs at 37° C. in a humidified chamber. After the coverslips were removed, slides were washed for 2 min in 0.4×SSC at 70° C., and then in 1× PBD (phosphate-buffered non-ionic detergent) for 2 min. Chromatin was counterstained in blue with 10 μl of 1% solution of 4',6'-diamidine-2-phenylindole (DAPI) in Vectashield antifade. Representative cells were captured using a computer-based imaging system (Quips XL Genetics Workstation, Vysis, Inc., Downers Grove, Ill.).

Q-cytogenetic studies were performed on each bone marrow specimen by analyzing 25 consecutive G-banded or Q-banded metaphases in which chromosomes 9 and 22 could be observed using the methods of Dewald et al, *Cancer Cytogenet.* 94:59 (1997). Hypermetaphase studies using single fusion probes for BCR and ABL1 (S-FISH) were done on many of these specimens using the methods of Seong et al, *Blood* 86:2343 (1995). D-FISH was performed using the directly labeled P5161-DC probe set to reveal two BCR/ABL1 fusion signals in cells with a t(9;22)(q34;q11.2); one on the abnormal chromosome 9 and the other on the abnormal chromosome 22. The ABL1 (600 kb) probe was directly labeled with Rhodamine Green (green signal) and included several DNA sequences that hybridized to 9 q34 and spanned the 200-Kb breakpoint region of ABL1 including additional normal chromosome sequence on each side of the breakpoint region. The BCR (500 Kb) probe was directly labeled with Texas Red (red signal) and included several DNA sequences that hybridized to 22q11.2 and spanned the common breakpoints in both the major and minor BCR as well as normal chromosome sequences on each side of the BCR gene breakpoint regions.

The specimens were studied in random order and in a blind fashion by two microscopists using strict scoring criteria for D-FISH. Dewald et al, *Blood* 31(9): 3357–3365 (1998). As referred to hereinafter, red BCR signals are referred to as R, green ABL1 signals as G, and BCR/ABL1 fusion signals as F. For scoring purposes, fusion signals were defined as merging or touching R and G signals. The scoring process was limited to normal nuclei with 2 R2 G, and abnormal nuclei with 1R1G2 F or 2R2G1F (one Ph chromosome), and 1R1G3F or 2R2G2F (two Ph chromosomes). For each specimen, each microscopist scored 250 consecutive qualifying interphase nuclei from different areas of the same slide. At the conclusion of the study, the inter-microscopist agreement was sufficient to pool their results on each specimen in subsequent analyses of the data. Thus, the final statistical analyses were based on 500 nuclei per specimen.

The normal range for D-FISH was calculated for peripheral blood specimens collected from 10 patients without any malignant hematologic disorder and for bone marrow specimens collected from 10 normal bone marrow transplant donors. The four serial dilutions were prepared by mixing cells from a normal individual and a Ph positive specimen to create a series of specimens determined by repeated blind studies to contain specified mean percentages of Ph positive nuclei.

The D-FISH results for each patient's specimens from both peripheral blood and bone marrow samples were calculated as the proportion of abnormal cells (number of abnormal cells per 500 scored cells). Since the proportion (p) of abnormal cells among the specimens ranged from 0 to 1 (i.e. 0–100%), a $\sin^{-1}(\sqrt{p})$ transformation was used to stabilize variances and provide a more nearly Gaussian distribution of values. Then, the differences (delta value) between bone marrow and peripheral blood in transformed proportions were computed for each patient's specimens. The proportion (p) of abnormal cells by Q-cytogenetics was also transformed to $\sin^{-1}(\sqrt{p})$.

The delta value for each paired-set of bone marrow and blood specimens was then analyzed using a repeated mea-

sures regression analysis (PROC MIXED in SAS) (19). For purposes of this statistical analysis, the approximate 4 month sampling intervals relative to commencement of therapy was considered a nominal predictor variable and the transformed proportion from Q-cytogenetics was included as a covariate. The within-patient correlation of delta values among respective specimen collection times was specified as an autocorrelation structure depending on the actual number of days between sampling times i.e., smaller correlations between sequential values for longer times between sampling episodes.

The classification scheme for response to therapy was based on Q-cytogenetics and was similar to the Italian Cooperative Group (Italian Cooperative Study Group on Chronic Myeloid Leukemia *New England Journal of Medicine* 30:820 (1994)) i.e., no response, minimal, minor, major and complete remission when 100%, 99–67%, 66–33%, 32–1% and 0% of metaphases are Ph positive, respectively.

Probe Sets in a D-FISH Assay Demonstrate Higher Sensitivity Than Standard Cytogenetic Testing

The goal was to study the effectiveness of the P5161-DC probes using 500 nuclei for each bone marrow and blood specimen. The goal for Q-cytogenetics was to study 25 metaphases from each bone marrow specimen. The goal for hypermetaphase studies was to study 200 metaphases from bone marrow. D-FISH was successful on 37/37 blood specimens and 37/37 bone marrow specimens. Q-cytogenetic was successful in 32/37 bone marrow specimens. Hypermetaphase was successful in 14/24 bone marrow specimens.

Very Low False Positive Rate (<1.0%)

Based on 500 nuclei from each of 10 normal bone marrow specimens, the mean percentage and standard deviation of nuclei with false BCR/ABL1 fusion was 0.1%±0.1 (range 0 to 1 per 500 nuclei). Based on 500 nuclei from each of 10 normal peripheral blood specimens, the mean percentage and standard deviation of nuclei with false BCR/ABL1 fusion was 0.04%±0.08. Based on this data, the upper bound of a one-sided 95% confidence interval for observing 1 to 500 (0.2%) neoplastic cells in either bone marrow or peripheral blood was calculated using the binomial distribution. For both bone marrow and peripheral blood, this calculation implied a cutoff greater than 4/500 (>0.8%) nuclei with BCR/ABL1 fusion to classify any specimen as abnormal.

Abnormal Reference Range for D-FISH in Untreated CML

The results of D-FISH for specimens from seven patients (nos. 2–7, 9) that were collected prior to treatment and that were not mosaic by Q-cytogenetic studies were used to establish an abnormal reference range. These specimens generally represent patients with untreated CML in clinical practice. Among these seven specimens, the mean percentage of abnormal cells was 97.6%±1.38 (range 95.4 to 99.0) for bone marrow, and 86.1%±13.59 (range 61.6 to 98.5) for blood.

Serial Dilutions

The observed percentage of neoplastic cells in each of the four serial dilution specimens was 97.6, 49.2, 8.2 and 1.8. The expected mean percentage of neoplastic cells in these specimens was 98.2, 49.1, 10.7, and 2.8, respectively. The difference between observed and expected values for each of these specimens was 0.6%, 0.1%, 2.5% and 1.0%, respectively.

Results of Using the Probe Set in a D-FISH Assay With Clinical Specimens

Results for Q-cytogenetic studies for bone marrow, and D-FISH for bone marrow and blood for each patient specimen are shown in FIG. 3. Based on Q-cytogenetics, three patients (nos. 4, 5 and 6) achieved a complete cytogenetic remission, one patient (no. 3) briefly achieved a major response and the rest of the patients were classified as minimal, minor or non-responders.

Each bone marrow specimen that had any abnormal metaphases by Q-cytogenetics was also abnormal for interphase nuclei by D-FISH in blood and bone marrow. Six specimens from three patients (nos. 4, 5 and 6) had only normal metaphases by Q-cytogenetics. For patient 6, D-FISH results were abnormal at 357 days in both bone marrow (4.8% abnormal nuclei) and blood (3.0% abnormal nuclei). For patient 5 at 262 days, the peripheral blood was marginally abnormal (1.0% abnormal nuclei) but bone marrow was within normal limits (0.6% abnormal nuclei). Each of the remaining four specimens with only normal metaphases by Q-cytogenetics were within normal limits for D-FISH in both bone marrow and blood.

Detection of Minimal Residual Disease States and Tracking Response to Therapy using the Probe Sets in FISH

Additional studies on the paired-sets of bone marrow and blood specimens that were normal by Q-cytogenetics and D-FISH were done to look for minimal residual disease. In a blind study, D-FISH was used to score 6,000 nuclei from four of the bone marrow specimens and five of the peripheral blood specimens in this series (Table 3, FIG. 9), and 3 blood and bone marrow specimens from normal individuals. In a separate study, the normal range for D-FISH for 6,000 nuclei was calculated to be <0.079%. Based on this cutoff, each of the normal blood and bone marrow specimens was correctly classified as normal. Three of the four patient bone marrow specimens and each of the patient peripheral blood specimens had minimal residual disease. It was not possible to do further studies on bone marrow no. 5 from patient 4 as this specimen had no leftover cells. The paired-blood specimen for this sampling time was in the abnormal range for D-FISH when 6,000 nuclei were studied and the bone marrow and one Ph positive metaphase among 169 metaphases that were examined by hypermetaphase FISH studies.

The actual proportions of neoplastic cells from bone marrow specimens were plotted against the corresponding proportions from peripheral blood samples (FIG. 2). The results imply that the proportion of abnormal cells from bone marrow specimens was typically greater (above $y=x$ line) than for peripheral blood.

For D-FISH, the mean 4 month inter-sample differences in percentage of abnormal nuclei between paired-sets of bone marrow and peripheral blood were not statistically different ($p>0.3$)(Table 4, FIG. 10). The deltas for D-FISH for peripheral blood were associated ($p<0.05$) with the transformed proportion of abnormal cells based on Q-cytogenetics of the paired bone marrow specimen. This is important because Q-cytogenetics of bone marrow is widely recognized as the "gold standard" for monitoring response to interferon therapy.

Based on these results, an additional regression analysis was done to develop a model for estimating the proportion of abnormal cells that would be obtained from bone marrow specimens using D-FISH results from peripheral blood samples. This is regression analysis of the data displayed in

FIG. 4, but used the transformed values of the proportions (FIG. 3). In FIG. 5, the dashed lines represent an approximate 95% confidence interval for a new predicted observation given a (new) peripheral blood value (prediction interval). This analysis indicated a significant ($p<0.001$) linear relationship and yields the following equation for estimating the proportion of abnormal cells in bone marrow

$$\text{specimens } (P_{BM}),\ \hat{P}_{BM}=[\sin\{0.1494+1.0324*\sin^{-1}(\sqrt{P_{PB}})\}]^2,$$

where P_{PB} is the proportion of abnormal cells based on D-FISH results in peripheral blood samples. This relationship is displayed in FIG. 6, and the numeric results for several choices of P_{PB} is listed in Table 5.

Discussion

The 4-month inter-sample changes in percentage of neoplastic nuclei in blood agreed closely with the corresponding intersample changes in percentage of neoplastic metaphases and nuclei in bone marrow over the course of interferon α-2b therapy. The reduction in percentage of Ph positive metaphases correlates with a prolonged chronic phase and increased survival in CML and the results of D-FISH on blood correlates with Q-cytogenetics. This demonstrates that using probes according to the present invention in a FISH assay is efficacious to test periodic peripheral blood specimens from patients with CML to monitor the effectiveness of interferon therapy. The analysis of 500 nuclei with the P5161-DC probe set in a D-FISH in bone marrow and peripheral blood detects <1% disease and is at least as sensitive as Q-cytogenetics. Thus, D-FISH analyses of interphase nuclei using probe constructs according to the present invention could substitute for Q-cytogenetics for purposes of monitoring response to therapy for CML. By analyzing 6,000 nuclei in specimens that were normal by Q-cytogenetics and by D-FISH based on analysis of 500 nuclei revealed evidence of residual disease was found (Table 4, FIG. 10). Thus, the methods and probe sets of the invention have the potential to detect very low levels of minimal disease in both blood and bone marrow.

In one other experiment that compares the results of FISH studies of paired-sets of bone marrow and peripheral blood to monitor therapy in CML, Muhlmann et al, *Genes, Chromosomes and Cancer* 21:90 (1998) used S-FISH to study 49 peripheral blood smears and 30 bone marrow specimens from 36 patients in chronic phase CML at different stages of cytogenetic remission. This experiment establishes that one can use whole blood as a comparative measure for events in the bone marrow.

The present invention precisely predicts the percentage of neoplastic nuclei in bone marrow based on data from blood. This should allow one to use blood to monitor therapy in clinical practice. The results presented in the present specification indicate that it is best to assess response to therapy based on changes in percentage of neoplastic nuclei using the same tissue over time. In other words, to compare D-FISH results among blood studies or among bone marrow studies, but not between blood and bone marrow studies. This is important because the percentage of abnormal nuclei in blood and bone marrow differs in most patients at most times before and after therapy (FIG. 4).

The results show a strong correlation between changes in the percentage of Ph positive metaphases by Q-cytogenetic studies over the course of therapy and changes in the percentage of interphase nuclei with BCR/ABL1 fusion in both blood and bone marrow. D-FISH using the probes of the invention was also useful to identify residual disease in both bone marrow and peripheral blood specimens for patients in complete cytogenetic remission. For patients on therapy, D-FISH could then be performed on peripheral blood at periodic intervals to assess the effectiveness of therapy. Consequently, bone marrow would not need to be collected to monitor therapy as frequently or at all as it is in current practice.

More details regarding scoring and correlation to clinical patients may be found in Dewald et al, Blood 31(9): 3357–3365 (1998).

EXAMPLE 3: CONSTRUCTION OF AML1/ETO DUAL FUSION PROBES

The AML1/ETO also called MTG8/CDR dual probes were assembled using the same method as in EXAMPLE 1 above. The highlights being illustrated below. The breakpoints are known to be clustered, Miyoshi et al (1991), Erickson et al (1992), Shimizu et al (1992), and Tighe et al (1993). The translocation has traditionally been detected using reverse transcriptase mediated polymerase chain reaction.

Two overlapping YACs, 902G10 and 903A9 were isolated from a total human library using an ETO cDNA probe. The YACs spanned the entire 8q22 breakpoint region. YAC C14B2 is predominantly located proximal to the 21q22 breakpoint region. YAC 925E1 was obtained from a total human library and includes a region located immediately distal to the breakpoint region.

The YAC DNAs 902G10 and 903A9 were labeled by nick translation with digoxigenin and C14B2 and 925E1 were labeled with biotin. FITC was used to detect biotin labeled probe molecules and rhodamine was used to detect digoxigenin labeled probe molecules using detection kits (Oncor, Inc.)

EXAMPLE 4: D-FISH FOR THE AML1/ETO TRANSLOCATION

The methods of Example 2 were repeated using the probe set of Example 3 with AML cell line Kasumi-1, lymphoblastoid cell line GM09948, bone marrow. Excellent results were obtained either two clear fusion signals being seen in a large percentage of cells. Details may be seen in Paskulin et al, Genes, Chromosomes & Cancer 21:144–151 (1998). The method of Example 2 is also performed on peripheral blood cells and correlated to the bone marrow data.

References cited herein are hereby incorporated by reference, and are listed below for convenience:

REFERENCES

Bentz, M., Cabot, G., Moos, M., Speicher, M. R., Ganser, A., Lichter, P. and Dohner, H. (1994) *Blood* 83: 1922.

Chumakov et al, *Nature* 377:175–197 (1995).

Dewald, GW, Juneau, AL, Schad, CR, Tefferi, A *Cancer Cytogenet.* 94:59 (1997).

Dewald et al, *Blood* 31(9): 3357–3365 (1998).

Fischer et al, *Blood* 88: 3962–3971 (1996).

Italian Cooperative Study Group on Chronic Myeloid Leukemia *New England Journal of Medicine* 30:820 (1994).

Kurzrock et al, *New England Journal of Medicine* 319:990 (1988).

Le Beau, *Blood* 81: 1979–1983 (1993).

Lion, T, Monitoring of Residual Disease in Chronic Myelogenous Leukaemia: Methodological Approaches and Clinical Aspects *Leukaemia* 10: 896 (1996).

Muhlmann, J., Thaler, H. Hilbe, W, Bechter, O, Erdel, M., Utermann, G. Duba, HC *Genes, Chromosomes and Cancer* 21:90.(1988).

Nakane et al, *Acta Histochem. Cytochem.* 20(2):229 (1987).

Pinkel et al, *Proc. Natl. Acad. Sci., U.S.A.* 83:2934–2938 (1986).

Paskulin et al, *Genes, Chromosomes & Cancer* 21:144–151 (1998).

Rudkin et al, *Nature* 265:472–3 (1977).

Sacchi et al, *Cancer Genetics and Cytogenetics* 79: 97–103 (1995)

Sinclair, P. B., Green, A. R., Grace, C., Nacheva, E. P., *Blood* 90:1395 (1997),

Seong, D C, Kantarjian, H M, Ro, J Y, Ralpaz, M, Xu, J. Robinson, J R, Deisseroth, A B, Champlin, R E, Siciliano, M J, *Blood* 86:2343 (1995).

The present invention is not to be limited in scope by the specific embodiments described herein. Indeed, various modifications of the invention in addition to those described herein will become apparent to those skilled in the art from the foregoing description and accompanying drawings. Such modifications are intended to fall within the scope of the appended claims.

Various publications are cited herein, the disclosures of which are incorporated by reference in their entireties.

What is claimed is:

1. A DNA probe set, said probe set comprising a first probe set and a second probe set,

said first probe set being sufficient in length and substantially complementary to an entire breakpoint region of a first DNA and nucleotides on both sides of the breakpoint region but less than an entire chromosome such that said first probe set will hybridize to both sides of the breakpoint region regardless of whether the first DNA has been broken in the breakpoint region and either end fused to another DNA, and

said second probe set being sufficient in length and substantially complementary to an entire breakpoint region of a second DNA and nucleotides on both sides of the breakpoint region but less than an entire chromosome such that said second probe set will hybridize to both sides of the breakpoint region regardless of whether the second DNA has been broken in the breakpoint region and either end fused to another DNA.

2. The probe set of claim **1**, wherein said probes are detectably labelled.

3. The probe set of claim **2**, wherein said first DNA is part of the ABL1 gene on chromosome 9 and the second DNA is part of the BCR gene on chromosome 22.

4. The probe set of claim **2**, wherein said first DNA is part of the AML1 gene on chromosome 21 and the second DNA is part of the ETO gene on chromosome 8.

5. A diagnostic kit for detecting a structural abnormality caused by chromosomal breakage and rearrangement containing a reagent comprising at least one probe set of the probe set according to claim **1**, and a container containing said reagent.

6. A diagnostic kit according to claim **5** further comprising at least two containers, wherein a first container contains a reagent comprising said first probe set and a second container contains a reagent comprising said second probe set.

7. A diagnostic kit according to claim **6** wherein said reagent comprises said first and said second probe set.

8. A DNA probe set, said probe set comprising a first probe set and a second probe set,

said first probe set being sufficient in length and substantially complementary to an entire breakpoint region of a first DNA and nucleotides on both sides of the breakpoint region but less than an entire chromosome such that said first probe set will hybridize to both sides of the breakpoint region regardless of whether a second DNA from a region other than the breakpoint region has been inserted in the breakpoint region, and

said second probe set being sufficient in length and substantially complementary to a 3' end and a 5' end of a second DNA but less than an entire chromosome such that said second probe set will hybridize to both ends of the second DNA regardless of whether the second DNA is inserted in the first DNA.

9. The probe set of claim **8**, wherein said probes are detectably labelled.

10. A DNA probe set, said probe set comprising a first probe set and a second probe set,

said first probe set being sufficient in length and substantially complementary to nucleotides on both sides of the breakpoint region of a first DNA but less than an entire chromosome such that said first probe set will hybridize to both sides of the breakpoint region regardless of whether the first DNA has been broken in the breakpoint region and either end fused to another DNA, and

said second probe set being sufficient in length and substantially complementary to nucleotides on both sides of the breakpoint region of a second DNA but less than an entire chromosome such that said second probe set will hybridize to both sides of the breakpoint region regardless of whether the second DNA has been broken in the breakpoint region and either end fused to another DNA.

11. The probe set of claim **10**, wherein said probes are detectably labeled.

12. The probe set of claim **11**, wherein said first DNA is part of the ABL1 gene on chromosome 9 and the second DNA is part of the BCR gene on chromosome 22.

13. The probe set of claim **11**, wherein said first DNA is part of the AML1 gene on chromosome 21 and the second DNA is part of the ETO gene on chromosome 8.

14. A diagnostic kit for detecting a structural abnormality caused by chromosomal breakage and rearrangement containing a reagent comprising at least one probe set of the probe set according to claim **10**, and a container containing said reagent.

15. A diagnostic kit according to claim **14** further comprising at least two containers, wherein a first container contains a reagent comprising said first probe set and a second container contains a reagent comprising said second probe set.

16. A diagnostic kit according to claim **15** wherein said reagent comprises said first and said second probe sets.

17. A diagnostic kit for detecting a structural abnormality caused by chromosomal breakage and rearrangement containing a reagent comprising at least one probe set of the probe set according to claim **8**, and a container containing said reagent.

18. A diagnostic kit according to claim **17** further comprising at least two containers, wherein a first container contains a reagent comprising said first probe set and a second container contains a reagent comprising said second probe set.

19. A diagnostic kit according to claim **18** wherein said reagent comprises said first and said second probe sets.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,414,133 B1
DATED : July 2, 2002
INVENTOR(S) : Jeanne Dietz-Band et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Drawings.

Figure 3, insert the sheet labeled "FIG. 3 Continued" which begins with the graph titled PT.4 immediately behind the first sheet of Figure 3, as shown on attached page.
Figure 3, insert the sheet labeled "FIG. 3 Continued" which begins with the graph titled PT.7 immediately behind the sheet labeled "FIG. 3 Continued" begins with the graph titled PT.4 as shown on attached page.
Figure 3, insert the sheet labeled "FIG. 3 Continued" which contains the graph titled PT.10 immediately behind the sheet labeled FIG. 3 Continued" which begins with the graph titled PT.7, as shown on attached page.

Signed and Sealed this

Twenty-ninth Day of July, 2003

JAMES E. ROGAN
Director of the United States Patent and Trademark Office

FIG. 3
CONTINUED

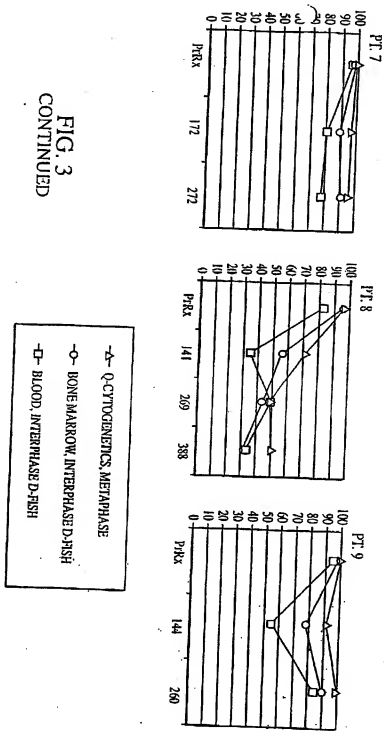


FIG. 3
CONTINUED

FIG. 3
CONTINUED

Day : Friday
Date: 3/26/2004

PALM INTRANET

Time: 09:37:40

Application Number Information

Application Number: **10/608092**
Assignments
Examiner Number: **67345 / MARSCHEL, ARDIN**
Filing Date: **06/30/2003**
Group Art Unit: **1631** **IFW IMAGE**
Effective Date: **06/30/2003**
Class/Subclass: **435/006.000**
Application Received: **06/30/2003**
Lost Case: **NO**
Patent Number:
Interference Number:
Issue Date: **00/00/0000**
Unmatched Petition: **NO**
Date of Abandonment: **00/00/0000**
L&R Code: Secrecy Code:**1**
Attorney Docket Number: **028723-384**
Third Level Review: **NO**
Secrecy Order: **NO**
Status: **172 /INTERFERENCE -- INITIAL MEMORANDUM**
Status Date: **03/09/2004**
Confirmation Number: **8136**
Oral Hearing: **NO**
Title of Invention: **CHROMOSOME-SPECIFIC STAINING TO DETECT GENETIC REARRANGEMENTS**

Bar Code	PALM Location	Location Date	Charge to Loc	Charge to Name	Employee Name	Location

Appln Info Contents | Petition Info | Atty/Agent Info | Continuity Data | Foreign Data | Inve

Search Another: Application# [ ] Search **or Patent#** [ ] Search
PCT / [ ] / [ ] Search **or PG PUBS #** [ ] Search
Attorney Docket # [ ] Search
Bar Code # [ ] Search

To go back use Back button on your browser toolbar.

Back to PALM | ASSIGNMENT | OASIS | Home page

Patent
Attorney Docket No. 028723-384

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of	
JOE W. GRAY et al	
Application No.: 10/608,092	Group Art Unit: 1655
Filed: June 30, 2003	Examiner: A. Marschel
For: A METHOD OF DETECTING GENETIC TRANSCLOCATIONS IDENTIFIED WITH CHROMOSOMAL ABNORMALITIES	

FAX received 9-9-03 PM

REQUEST BY APPLICANTS FOR INTERFERENCE PURSUANT TO 37 CFR 1.607

Honorable Commissioner of Patents and Trademarks
Washington, D.C. 20231

Sir:

Applicants respectfully request that an interference be declared between the application identified in caption and U.S. Patent No. 6,414,133[1] ("the '133 patent"). Applicants respectfully point out that examination of the present application should "be conducted with special dispatch" because it requests an interference with an issued patent. 37 CFR 1.607(b); MPEP 708.01 and 2307.

As explained in detail below, Applicants request that the interference be declared:

(i) Employing the proposed Count set forth in attached Appendix A;

(ii) With claims 1-3, 5-12, and 14-19 of the '133 patent and claims 127-143 of the present application designated as corresponding to the Proposed Count; and

[1] The '133 patent was submitted in the IDS filed on 26 August 2003.

(iii) Applicants indicated to be entitled to the benefit of application Serial No. 07/537,305 filed June 12, 1990[2].

Further, upon a determination by the Examiner that an interference should be declared, immediate issuance of a Notice suspending prosecution pending declaration of an interference is respectfully requested.

In support of the Request for Interference, Applicants present below sections (1)-(6) corresponding to the sections of 37 CFR 1.607.

(1) Identifying the patent

The patent against which Applicants request an interference is U.S. Patent No. 6,414,133 which lists as inventors Jeanne Dietz-Band, Wang-Ting Hsieh, and John F. Connaughton. The patent issued July 2, 2002, and is assigned on its face to Ventana Medical Systems, Inc. The patent was issued on application Serial No. 09/170,630, filed October 13, 1998. Because the instant application claims priority from application Serial No. 07/537,305, filed June 12, 1990, the present Applicants should be designated Senior Party, and Dietz-Band et al. should be designated Junior Party.

(2) Presentation of a proposed Count

Applicants propose a Count as follows:

A DNA probe set, said probe set comprising a first probe set and a second probe set,

[2] The present application is a divisional of application Serial No. 08/487,974, filed June 7, 1995, which is a continuation of 08/342,028, filed November 16, 1994 (now abandoned), which is a continuation of application Serial No. 08/181,367, filed January 14, 1994 (now abandoned), which is a continuation of application Serial No. 08/054,353, filed April 28, 1993 (abandoned), which is a continuation of application Serial No. 07/537,305, filed June 12, 1990. While the application previously claimed the benefit of earlier applications, the priority claim has been amended to reflect the proper priority claim for the claims pending in the present application.

said first probe set being sufficient in length and substantially complementary to an entire breakpoint region of a first DNA and nucleotides on both sides of the breakpoint region but less than an entire chromosome such that said first probe set will hybridize to both sides of the breakpoint region regardless of whether the first DNA has been broken in the breakpoint region and either end fused to another DNA, and

said second probe set being sufficient in length and substantially complementary to an entire breakpoint region of a second DNA and nucleotides on both sides of the breakpoint region but less than an entire chromosome such that said second probe set will hybridize to both sides of the breakpoint region regardless of whether the second DNA has been broken in the breakpoint region and either end fused to another DNA;

wherein said probes are detectably labeled; and

wherein said first DNA is part of the ABL1 gene on chromosome 9 and the second DNA is part of the BCR gene on chromosome 22.

The proposed Count is also presented in Appendix A.

Applicants note, pursuant to 37 CFR 1.606, that the proposed Count is identical to claim 3 of the '133 patent, written in independent form, and to claim 129 of the present application, written in independent form.

(3) Identification of claims in the '133 patent corresponding to the proposed Count

According to 37 CFR 1.606, "[a]ll claims in the application and patent which define the same patentable invention as a count shall be designated to correspond to the count." "Same patentable invention" is defined by 37 CFR 1.601(n), which states

> (n) Invention "A" is the *same patentable invention* as invention "B" when invention "A" is the same as (35 U.S.C. 102) or is obvious (35 U.S.C. 103) in view of invention "B" assuming invention "B" is prior art with respect to invention "A". Invention "A" is a *separate patentable invention* with respect to invention "B" when invention "A" is new (35 U.S.C. 102) and non-obvious (35 U.S.C. 103) in view of invention "B" assuming invention "B" is prior art with respect to invention "A".

Claims 1-3, 5-12, and 14-19 of the '133 patent, correspond to the proposed Count.

Claim 3

The proposed Count is identical to claim 3 of the '133 patent.

Claim 2

Claim 2 is directed to the probe set of claim 1, wherein the probes are detectably labeled. Claim 2 defines a genus from which claim 3 depends. Consequently, if claim 3 were prior art to Claim 2, it would anticipate claim 2. *In re Slayter,* 275 F.2d 408, 411, 125 USPQ 345, 347 (CCPA 1960)("A generic claim cannot be allowed to applicant if the prior art discloses a species falling within the claimed genus."); *In re Gostell,* 872 F.2d 1008, 10 USPQ2d 1614 (Fed. Cir. 1989). In addition, Dietz-Band admits, at col 9, lines 4-32 of the '133 patent, that detectable labels for probes, and methods of labeling probes, are known in the art. Claim 2 is thus directed to the same patentable invention as claim 3 and the Count, and so corresponds to the proposed Count.

Claim 1

Likewise, as claim 2 depends from claim 1, claim 3 is a species of the genus defined by claim 1. Consequently, if claim 3 were prior art to claim 1, it would anticipate claim 1. Claim 1 is thus directed to the same patentable invention as claim 3 and the Count, and so corresponds to the proposed Count.

Claim 5

Claim 5 is directed to a kit comprising a probe set according to claim 1. Kits are conventional in the art. For example, the 1988 Stratagene Catalog, at p. 39 (Appendix C), motivates and suggests that the assemblage of materials into kits which may be pre-mixed for the benefits therein cited such as availability and quality testing etc. Kits are also well known in biochemical work with either individual or mixed components ready for use. Thus it would have

been obvious to one of ordinary skill in the art at the time of the filing of the '133 patent, in possession of the probe set of claim 1, to assemble the components of that probe set into a kit as suggested by the Stratagene Catalog. As claim 5 is obvious over claim 1, it is likewise obvious over claim 3 and the proposed Count for the reasons discussed above in connection with claim 1.

Claim 6

Claim 6 is directed to a diagnostic kit according to claim 5, comprising at least two containers, each of which contains a reagent comprising a probe set according to claim 1. Claim 6 is obvious over claims 5, 1, and 3, and the proposed Count, for the reasons discussed in connection with claim 5, above.

Claim 7

Claim 7 is directed to a diagnostic kit according to claim 6, wherein the recited reagent contains both the first and second probe set according to claim 1. Claim 7 is obvious over claim 3 and the proposed Count, for the reasons discussed in connection with claims 5 and 6 above.

Claim 8

Claim 8 is worded similarly to claim 1. A side-by-side comparison of claims 1 and 8 is shown below.

1. A DNA probe set, said probe set comprising a first probe set and a second probe set,	8. A DNA probe set, said probe set comprising a first probe set and a second probe set,
said first probe set being sufficient in length and substantially complementary to an entire breakpoint region of a first DNA and	said first probe set being sufficient in length and substantially complementary to an entire breakpoint region of a first DNA and

nucleotides on both sides of the breakpoint region but less than an entire chromosome such that said first probe set will hybridize to both sides of the breakpoint region regardless of whether **the first DNA has been broken in the breakpoint region and either end fused to another DNA, and**	nucleotides on both sides of the breakpoint region but less than an entire chromosome such that said first probe set will hybridize to both sides of the breakpoint region regardless of whether **a second DNA from a region other than the breakpoint region has been inserted in the breakpoint region, and**
said second probe set being sufficient in length and substantially complementary to **an entire breakpoint region of a second DNA and nucleotides on both sides of the breakpoint region** but less than an entire chromosome such that said second probe set will hybridize **to both sides of the breakpoint region** regardless of whether the second DNA **has been broken in the breakpoint region and either end fused to another DNA.**	said second probe set being sufficient in length and substantially complementary to **a 3' end and a 5' end of a second DNA** but less than an entire chromosome such that said second probe set will hybridize **to both ends of the second DNA** regardless of whether the second DNA **is inserted in the first DNA.**

Claim 1 relates to a probe set which is useful in detecting a particular type of chromosomal rearrangement, called a translocation, in which genetic material is exchanged between two chromosomes. Two probe sets are provided, each of which is substantially complementary to a breakpoint region of a particular DNA. Claim 8 relates to a probe set that is useful in detecting a different type of chromosomal translocation, an insertion, in which a piece of a chromosome is inserted into another chromosome.

However, when the claims are stripped of functional language, it can be seen that the probe sets recited claims 1 and 8 are substantially identical, and where they differ, claim 1 is narrower than -- indeed is a species of -- claim 8. The first probe set of claim 1 is required to be "sufficient in length and substantially complementary to an entire breakpoint region of a first DNA and nucleotides on both sides of the breakpoint region but less than an entire chromosome." Claim 8 uses exactly the same description of the first probe set in that claim.

The second probe set of claim 1, like the first probe set, is required to be "sufficient in length and substantially complementary to *an entire breakpoint region* of a second DNA and nucleotides on both sides of the breakpoint region but less than an entire chromosome."

(Emphasis added) In contrast, the second probe set of claim 8 is required to be "sufficient in length and substantially complementary to *a 3' end and a 5' end* of a second DNA but less than an entire chromosome." (Emphasis added) It will be readily apparent that "an entire breakpoint region," like any DNA, will necessarily have a 3' and a 5' end, as required by claim 8. However, not all DNA molecules with 3' and 5' ends will represent an entire breakpoint region, as required by claim 1. Thus the second probe set of claim 1 represents a *species* of the genus of claim 8, that would anticipate claim 8 if it were prior art to claim 8. Claim 8 thus represents the same patentable invention as claim 1, and claim 3, and the proposed count.

Claim 9

Claim 9 depends from claim 8, but adds the limitation that the probes are detectably labeled. As noted above, Dietz-Band admits, at col 9, lines 4-32 of the '133 patent, that detectable labels for probes, and methods of labeling probes, are known in the art. As claim 3 (and the proposed Count) also incorporate this limitation, claim 9 is obvious in view of claim 3 and the proposed Count for the same reasons set forth above in connection with claim 8.

Claim 10

Claim 10 is worded similarly to claim 1. A side-by-side comparison of claims 1 and 10 is shown below.

1. A DNA probe set, said probe set comprising a first probe set and a second probe set,	10. A DNA probe set, said probe set comprising a first probe set and a second probe set,
said first probe set being sufficient in length and substantially complementary to **an entire breakpoint region of a first DNA** and nucleotides on both sides of the breakpoint region but less than an entire chromosome such that said first probe set will hybridize to both sides of the breakpoint region regardless of	said first probe set being sufficient in length and substantially complementary to **nucleotides on both sides of the breakpoint region of** a first DNA but less than an entire chromosome such that said first probe set will hybridize to both sides of the breakpoint region regardless of

whether the first DNA has been broken in the breakpoint region and either end fused to another DNA, and	whether a second DNA from a region other than the breakpoint region has been inserted in the breakpoint region, and
said second probe set being sufficient in length and substantially complementary to **an entire breakpoint region of a second DNA and nucleotides on both sides of the breakpoint region** but less than an entire chromosome such that said second probe set will hybridize to both sides of the breakpoint region regardless of whether the second DNA has been broken in the breakpoint region and either end fused to another DNA.	said second probe set being sufficient in length and substantially complementary to **nucleotides on both sides of the breakpoint region of a second DNA** but less than an entire chromosome such that said second probe set will hybridize to both sides of the breakpoint region regardless of whether the second DNA has been broken in the breakpoint region and either end fused to another DNA.

Dietz-Band claim 1 is identical to claim 10 in all but one limitation. Claim 10 requires that the first and second probe sets are complementary to "nucleotides on both sides of the breakpoint region" of the first and second DNA molecules. Claim 1 requires that the first and second probe sets are complementary to "an *entire* breakpoint region . . . and nucleotides on both sides of the breakpoint region."

Any probe set that is complementary to an entire breakpoint region will necessarily be complementary to nucleotides on both sides of the breakpoint region. Consequently, every probe set that meets the limitations of claim 1 will also meet the limitations of claim 10. Thus claim 10 represents a genus of probe sets of which claim 1 is a subset. Claim 1 is thus directed to the same patentable invention as claim 10 because claim 1 would anticipate claim 10 if it were prior art to claim 10. As claim 3 is a species of claim 1, claim 3 is likewise a species of claim 10. Consequently, claim 10 is directed to the same patentable invention as claim 3, and the proposed Count.

Claim 11

Claim 11 depends from claim 10, but adds the limitation that the probes are detectably labeled. As noted above, Dietz-Band admits, at col 9, lines 4-32 of the '133 patent, that detectable labels for probes, and methods of labeling probes, are known in the art. As claim 3

(and the proposed Count) also incorporate this limitation, claim 11 is obvious in view of claim 3 and the proposed Count for the same reasons set forth above in connection with claim 10.

Claim 12

Claim 12 depends from claims 11 (and thus from claim 10), but adds the limitation that "said first DNA is part of the ABL1 gene on chromosome 9" and that "the second DNA is part of the BCR gene on chromosome 22." Dietz-Band admits, at col 1, lines 22-33 of the '133 patent, that breakpoints in the ABL1 gene on chromosome 9 and the BCR gene on chromosome 22 are known in the art to be characteristic of CML. As claim 3 (and the proposed Count) also incorporate these limitations, claim 12 is obvious in view of claim 3 and the proposed Count for the same reasons set forth above in connection with claims 11 and 10.

Claim 14

Claim 14 is directed to a kit comprising a probe set according to claim 10. Kits are conventional in the art. For example, the 1988 Stratagene Catalog. at p. 39, motivates and suggests that the assemblage of materials into kits which may be pre-mixed for the benefits therein cited such as availability and quality testing etc. Kits are also well known in biochemical work with either individual or mixed components ready for use. Thus it would have been obvious to one of ordinary skill in the art at the time of the filing of the '133 patent, in possession of the probe set of claim 10, to assemble the components of that probe set into a kit as suggested by the Stratagene Catalog. As claim 14 is obvious over claim 10, it is likewise obvious over claim 3 and the proposed Count for the reasons discussed above in connection with claim 10.

Claim 15

Claim 15 is directed to a diagnostic kit according to claim 14, comprising at least two containers, each of which contains a reagent comprising a probe set according to claim 10. Claim 15 is obvious over claims 14, 10, and 3, and the proposed Count, for the reasons discussed in connection with claim 14, above.

Claim 16

Claim 16 is directed to a diagnostic kit according to claim 15, wherein the recited reagent contains both the first and second probe set according to claim 10. Claim 16 is obvious over claim 3 and the proposed Count, for the reasons discussed in connection with claims 14 and 15 above.

Claim 17

Claim 17 is directed to a kit comprising a probe set according to claim 8. Kits are conventional in the art. For example, the 1988 Stratagene Catalog. at p. 39, motivates and suggests that the assemblage of materials into kits which may be pre-mixed for the benefits therein cited such as availability and quality testing etc. Kits are also well known in biochemical work with either individual or mixed components ready for use. Thus it would have been obvious to one of ordinary skill in the art at the time of the filing of the '133 patent, in possession of the probe set of claim 8, to assemble the components of that probe set into a kit as suggested by the Stratagene Catalog. As claim 17 is obvious over claim 8, it is likewise obvious over claim 3 and the proposed Count, for the reasons discussed above in connection with claim 8.

Claim 18

Claim 18 is directed to a diagnostic kit according to claim 17, comprising at least two containers, each of which contains a reagent comprising a probe set according to claim 8. Claim 18 is obvious over claims 17, 8, and 3, and the proposed Count, for the reasons discussed in connection with claim 17, above.

Claim 19

Claim 19 is directed to a diagnostic kit according to claim 18, wherein the recited reagent contains both the first and second probe set according to claim 8. Claim 19 is obvious over claim 3 and the proposed Count, for the reasons discussed in connection with claims 17 and 18 above.

(4) Presentation of claims corresponding to the proposed Count and explanation why such claims correspond to the proposed Count

Claims 127-143 correspond to the proposed Count. It will be readily appreciated that claim 129 and the proposed Count are identical and therefore, Claim 129 corresponds to the proposed Count. As claims 127-143 are substantially identical to Dietz-Band claims 1-3, 5-12, and 13-19, Applicants submit that claims 127-143 of the instant application correspond to the proposed Count for the reasons set forth in the discussion of the Dietz-Band claims above.

(5) Applying terms of application claims to the disclosure of the application

Attached hereto as Appendix B is a chart providing an element-by-element recitation of the claims of the present application and an indication of exemplary passages in the application where, at the very least, the claims find full support. Applicants emphasize that this support set forth in this chart is only exemplary, and reserve the right to supplement the support for each claim as necessary or desired.

(6) The Requirements of 35 USC 135(b)(1) Are Satisfied.

Section (b)(1) of 35 USC 135 requires that

> A claim which is the same as, or for the same or substantially the same subject matter as, a claim of an issued patent may not be made in any application unless such a claim is made prior to one year from the date on which the patent was granted.

The pending claims in the present application were added by Applicants' Preliminary Amendment filed June 30, 2003. As this is less than one year after the issuance of the '133 patent on July 2, 2002, the terms of 35 USC 135(b)(1) are satisfied.

(7) Conclusion

Applicants respectfully request that examination of the present application be expedited. Applicants also request that an interference be declared:

(i) employing the proposed Count set forth in attached Appendix A;

(ii) with claims 1-3, 5-12, and 14-19 of the '133 patent and claims 127-143 of the present application designated as corresponding to the proposed Count; and

(iii) Applicants indicated to be entitled to benefit of the applications listed in footnote 2, above.

Further, upon a determination by the Examiner that an interference should be declared, issuance of a Notice suspending prosecution pending declaration of an interference is respectfully requested. The above actions are respectfully requested.

Respectfully submitted,

By: Malcolm K. McGowan

R. Danny Huntington; Registration No. 27,903
Malcolm K. McGowan, Ph.D.; Registration No. 39,300

Burns, Doane, Swecker & Mathis
P.O. Box 1404
Alexandria, VA 22313-1404
(703) 836-6620

Dated: 9 September 2003

APPENDIX A
Proposed Count

A DNA probe set, said probe set comprising a first probe set and a second probe set,

said first probe set being sufficient in length and substantially complementary to an entire breakpoint region of a first DNA and nucleotides on both sides of the breakpoint region but less than an entire chromosome such that said first probe set will hybridize to both sides of the breakpoint region regardless of whether the first DNA has been broken in the breakpoint region and either end fused to another DNA, and

said second probe set being sufficient in length and substantially complementary to an entire breakpoint region of a second DNA and nucleotides on both sides of the breakpoint region but less than an entire chromosome such that said second probe set will hybridize to both ends of the breakpoint region regardless of whether the second has been broken in the breakpoint region and either end fused to another DNA

wherein said probes are detectably labeled, and

wherein said first DNA is part of the ABL1 gene on chromosome 9 and the second DNA is part of the BCR gene on chromosome 22.

APPENDIX B

Exemplary support for the claims in 10/608,092, filed June 30, 2003[3]

CLAIMS - US 6,414,133 (DIETZ-BAND)	PENDING CLAIMS	EXEMPLARY SUPPORT IN SPEC.
1. A DNA probe set, said probe set comprising a first probe set and a second probe set,	127. A DNA probe set, said probe set comprising a first probe set and a second probe set,	"In particular, chromosome specific staining reagents are provided which comprise heterogeneous mixtures of nucleic acid fragments, each fragment having a substantial fraction of its sequences substantially complementary to a portion of the nucleic acid for which specific staining is desired — the target nucleic acid, preferably the target chromosomal material. In general, the nucleic acid fragments are labeled by means as exemplified herein and indicated infra." *p. 18, lines 14-20; ¶ 0071.* "Several different high complexity probes, each labeled by a different method, can be used simultaneously. The binding of different probes can thereby be distinguished, for example, by different colors." *p. 74, lines 15-17; ¶ 0246.*
said first probe set being sufficient in length and substantially complementary to an entire breakpoint region of a first DNA and nucleotides on both sides of the breakpoint region but less than an entire chromosome such that said first probe set will hybridize to both sides of the breakpoint region regardless of whether the first DNA has been broken in the breakpoint region and either end fused to another DNA, and	said first probe set being sufficient in length and substantially complementary to an entire breakpoint region of a first DNA and nucleotides on both sides of the breakpoint region but less than an entire chromosome such that said first probe set will hybridize to both sides of the breakpoint region regardless of whether the first DNA has been broken in the breakpoint region and either end fused to another DNA, and	"The invention provides for nucleic acid probes that reliably stain targeted chromosomal materials in the vicinity of one or more suspected genetic rearrangements. . . . Such nucleic acid probes preferably comprise nucleic acid sequences that are substantially homologous to nucleic acid sequences in chromosomal regions that flank and/or extend partially or fully across breakpoints associated with genetic rearrangements." *p. 19, lines 11-18; ¶ 0073.* "As indicated above, with current

[3] Applicants reserve the right to supplement this table as necessary or desirable.

APPENDIX B

CLAIMS - US 6,414,133 (DIETZ-BAND)	PENDING CLAIMS	EXEMPLARY SUPPORT IN SPEC.
		hybridization techniques it is possible to obtain a reliable, easily detectable signal with a probe of about 40 to about 100 kb (e.g. the probe insert capacity of one or a few cosmids) targeted to a compact point in the genome. Thus, for example, a complexity in the range of approximately 100 kb now permits hybridization to both sides of a tumor-specific translocation. The portion of the probe targeted to one side of the breakpoint can be labeled differently from that targeted to the other side of the breakpoint so that the two sides can be differentiated with different colors, for example." p. 38, lines 8-16; ¶ 0141. "32. High complexity nucleic acid probes for the detection of genetic rearrangements. 111. Nucleic acid probes, according to claim 32, comprising nucleic acid sequences that are substantially homologous to nucleic acid sequences in chromosomal regions that flank and/or extend partially or fully across breakpoints associated with cytogenetically similar but genetically different diseases." Original claims 32 and 111 See also, Fig. 11, and description below

APPENDIX B

CLAIMS - US 6,414,133 (DIETZ-BAND)	PENDING CLAIMS	EXEMPLARY SUPPORT IN SPEC.
said second probe set being sufficient in length and substantially complementary to an entire breakpoint region of a second DNA and nucleotides on both sides of the breakpoint region but less than an entire chromosome such that said second probe set will hybridize to both sides of the breakpoint region regardless of whether the second DNA has been broken in the breakpoint region and either end fused to another DNA.	said second probe set being sufficient in length and substantially complementary to an entire breakpoint region of a second DNA and nucleotides on both sides of the breakpoint region but less than an entire chromosome such that said second probe set will hybridize to both sides of the breakpoint region regardless of whether the second DNA has been broken in the breakpoint region and either end fused to another DNA.	see above; also "Figure 11 illustrates some exemplary probe strategies for detection of structural aberrations. . . . Section a) represents the use of a probe which stains a whole chromosome . . . . Section b) represents the reduction of the stained region of the chromosome shown in a) to that in the vicinity of a breakpoint . . . Section c) represents the use of a probe which binds to sequences which come together as a result of the rearrangement and allows for the detection in metaphase and interphase cells. In this case the different sequences are stained with different 'colors.' Such a staining pattern is that used in the examples of Section VIII of this application . . .. Section d) represents an extension of c) by including staining of both sides of both breakpoints involved in the rearrangement. Different 'colors' are used as indicated. The additional information supplied by the more complex staining pattern may assist with interpretation of the nuclei." p. 31, line 1 - p. 32, line 19; ¶ 0122-0127.

APPENDIX B

CLAIMS - US 6,414,133 (DIETZ-BAND)	PENDING CLAIMS	EXEMPLARY SUPPORT IN SPEC.
2. The probe set of claim 1, wherein said probes are detectably labeled.	128. The probe set of claim 127, wherein said probes are detectably labeled.	"Section III *infra* describes methods of rendering the probe visible. Since multiple compatible methods of probe visualization are available, the binding patterns of different components of the probe can be distinguished — for example, by color. Thus, this invention is capable of producing any desired staining pattern on the chromosomes visualized with one or more colors (a multi-color staining pattern) and/or other indicator methods." *p. 36, lines 17-23; ¶ 0137.* See also, *Section III. "Labeling the Nucleic Acid Fragments of the Heterogeneous Mixture," at pp 72-74; ¶. 0241-0246.*

APPENDIX B

CLAIMS - US 6,414,133 (DIETZ-BAND)	PENDING CLAIMS	EXEMPLARY SUPPORT IN SPEC.
3. The probe set of claim 2, wherein said first DNA is part of the ABL1 gene on chromosome 9 and the second DNA is part of the BCR gene on chromosome 22.	129. The probe set of claim 128, wherein said first DNA is part of the ABL1 gene on chromosome 9 and the second DNA is part of the BCR gene on chromosome 22.	"Specifically herein exemplified are chromosome specific reagents and methods to detect genetic rearrangements . . . that produce the BCR-ABL fusion which is diagnostic for chronic myelogenous leukemia (CML). Such chromosome specific reagents for the diagnosis of CML contain nucleic acid sequences which are substantially homologous to chromosomal sequences in the vicinity of the translocation breakpoint regions of chromosomal regions 9q34 and 22q11 associated with CML. Those reagents produce a staining pattern which is distinctively altered when the BCR-ABL fusion characteristic of CML occurs. Figure 11 graphically demonstrates a variety of staining patterns which, along with other potential staining patters, are altered in the presence of a genetic rearrangement, such as, the BCR-ABL fusion." *p. 19, line 22 - p. 20, line 8; ¶ 0075-0076.* "Figure 8 illustrates the locations of probes to the CML breakpoint and corresponding pattern of staining in both normal and CML metaphase and interphase nuclei. The left side shows schematic representations of the BCR gene on chromosome 22, the ABL gene of chromosome 9, and the BCR-ABL fusion gene on the Philadelphia chromosome. Also shown are the locations of CML breakpoints and their relation to the probes (32). " *p. 29, line 24 - p. 30, line 6; ¶ 118-119.*

APPENDIX B

CLAIMS - US 6,414,133 (DIETZ-BAND)	PENDING CLAIMS	EXEMPLARY SUPPORT IN SPEC.
5. A diagnostic kit for detecting a structural abnormality caused by chromosomal breakage and rearrangement containing a reagent comprising at least one probe set of the probe set according to claim 1, and a container containing said reagent.	130. A diagnostic kit for detecting a structural abnormality caused by chromosomal breakage and rearrangement containing a reagent comprising at least one probe set of the probe set according to claim 127, and a container containing said reagent.	"This invention still further provides for test kits comprising appropriate nucleic acid probes for use in tumor cytogenetics, in the detection of disease related loci, in the analysis of structural abnormalities, for example translocations, among other genetic rearrangements, and for biological dosimetry." *p. 25, lines 8-12; ¶ 0095.*
6. A diagnostic kit according to claim 5 further comprising at least two containers, wherein a first container contains a reagent comprising said first probe set and a second container contains a reagent comprising said second probe set.	131. A diagnostic kit according to claim 130 further comprising at least two containers, wherein a first container contains a reagent comprising said first probe set and a second container contains a reagent comprising said second probe set.	*See claim 130, above*
7. A diagnostic kit according to claim 6 wherein said reagent comprises said first and said second probe set.	132. A diagnostic kit according to claim 131 wherein said reagent comprises said first and said second probe set.	*See claim 131, above*
8. A DNA probe set, said probe set comprising a first probe set and a second probe set,	133. A DNA probe set, said probe set comprising a first probe set and a second probe set,	"In particular, chromosome specific staining reagents are provided which comprise heterogeneous mixtures of nucleic acid fragments, each fragment having a substantial fraction of its sequences substantially complementary to a portion of the nucleic acid for which specific staining is desired — the target nucleic acid, preferably the target chromosomal material. In general, the nucleic acid fragments are labeled by means as exemplified herein and indicated infra." p. 18, lines 14-20
said first probe set being sufficient in length and substantially complementary to an entire breakpoint region of a first DNA and nucleotides on both sides of the breakpoint region but less than an entire chromosome such that said first probe set will hybridize to	said first probe set being sufficient in length and substantially complementary to an entire breakpoint region of a first DNA and nucleotides on both sides of the breakpoint region but less than an entire chromosome such that said first probe set will hybridize to	"As indicated above, with current hybridization techniques it is possible to obtain a reliable, easily detectable signal with a probe of about 40 to about 100 kb (eg. the probe insert capacity of one or a few cosmids) targeted to a compact point in the

APPENDIX B

CLAIMS - US 6,414,133 (DIETZ-BAND)	PENDING CLAIMS	EXEMPLARY SUPPORT IN SPEC.
both sides of the breakpoint region regardless of whether a second DNA from a region other than the breakpoint region has been inserted in the breakpoint region, and	both sides of the breakpoint region regardless of whether a second DNA from a region other than the breakpoint region has been inserted in the breakpoint region, and	genome. Thus, for example, a complexity in the range of approximately 100 kb now permits hybridization to both sides of a tumor-specific translocation. The portion of the probe targeted to one side of the breakpoint can be labeled differently from that targeted to the other side of the breakpoint so that the two sides can be differentiated with different colors, for example." *p. 38, lines 8-16; ¶0141.* "32. High complexity nucleic acid probes for the detection of genetic rearrangements. 111. Nucleic acid probes, according to claim 32, comprising nucleic acid sequences that are substantially homologous to nucleic acid sequences in chromosomal regions that flank and/or extend partially or fully across breakpoints associated with cytogenetically similar but genetically different diseases." Original claims 32 and 111 See also, Fig. 11, and description below
said second probe set being sufficient in length and substantially complementary to a 3' end and a 5' end of a second DNA but less than an entire chromosome such that said second probe set will hybridize to both ends of the second DNA regardless of whether the second DNA is inserted in the first DNA.	said second probe set being sufficient in length and substantially complementary to a 3' end and a 5' end of a second DNA but less than an entire chromosome such that said second probe set will hybridize to both ends of the second DNA regardless of whether the second DNA is inserted in the first DNA.	see above; also "The invention concerns chromosome specific reagents and methods of staining targeted chromosomal material that is in the vicinity of a suspected genetic rearrangement. Such genetic rearrangement include but are not limited to . . . insertions" *p. 19, lines 3-7; ¶0072.* "Figure 9 shows a fluorescence in-situ hybridization (FISH) in metaphase spreads and interphase nuclei . . . Panel D shows that abl staining is interstitial on the derivative 22

APPENDIX B

CLAIMS - US 6,414,133 (DIETZ-BAND)	PENDING CLAIMS	EXEMPLARY SUPPORT IN SPEC.
		chromosome arising from an insertional event in a case of CMP with 46XY tNS (22:9) (q11;q34)." *p. 30, lines 7-15; ¶ 0121.* "Figure 11 illustrates some exemplary probe strategies for detection of structural aberrations . . . Section d) represents an extension of c) by including staining of both sides of both breakpoints involved in the rearrangement. Different 'colors' are used as indicated. The additional information supplied by the more complex staining pattern may assist with interpretation of the nuclei. It might also permit recognition of an apparent insertional event as discussed herein." *p. 31, line 1 – p. 32, line 21; ¶ 0122-0127.* "One case (CML-6) was suspected by classical cytogenetics to have an insertion of chromosomal material at 22q11. Dual color hybridization to metaphase spreads from this case showed the red-green pair to be centrally located in a small chromosome (Figure 9D). That result is consistent with the formation of the BCR-ABL fusion gene by an insertion." *p. 122, lines 6-10; ¶ 0354.*

APPENDIX B

CLAIMS - US 6,414,133 (DIETZ-BAND)	PENDING CLAIMS	EXEMPLARY SUPPORT IN SPEC.
9. The probe set of claim 8, wherein said probes are detectably labeled.	134. The probe set of claim 133, wherein said probes are detectably labeled.	"Section III *infra* describes methods of rendering the probe visible. Since multiple compatible methods of probe visualization are available, the binding patterns of different components of the probe can be distinguished — for example, by color. Thus, this invention is capable of producing any desired staining pattern on the chromosomes visualized with one or more colors (a multi-color staining pattern) and/or other indicator methods." *p. 36, lines 17-23, ¶ 0137.* See also, *Section III. "Labeling the Nucleic Acid Fragments of the Heterogeneous Mixture," at pp 72-74; ¶ 0241-0246.*
10. A DNA probe set, said probe set comprising a first probe set and a second probe set,	135. A DNA probe set, said probe set comprising a first probe set and a second probe set,	"In particular, chromosome specific staining reagents are provided which comprise heterogeneous mixtures of nucleic acid fragments, each fragment having a substantial fraction of its sequences substantially complementary to a portion of the nucleic acid for which specific staining is desired — the target nucleic acid, preferably the target chromosomal material. In general, the nucleic acid fragments are labeled by means as exemplified herein and indicated infra." *p. 18, lines 14-20; ¶ 0071.*
said first probe set being sufficient in length and substantially complementary to nucleotides on both sides of the breakpoint region of a first DNA but less than an entire chromosome such that said first probe set will hybridize to both sides of the breakpoint region regardless of whether the first DNA has been broken in the breakpoint region and either end fused to another DNA, and	said first probe set being sufficient in length and substantially complementary to nucleotides on both sides of the breakpoint region of a first DNA but less than an entire chromosome such that said first probe set will hybridize to both sides of the breakpoint region regardless of whether the first DNA has been broken in the breakpoint region and either end fused to another DNA, and	"As indicated above, with current hybridization techniques it is possible to obtain a reliable, easily detectable signal with a probe of about 40 to about 100 kb (eg. the probe insert capacity of one or a few cosmids) targeted to a compact point in the genome. Thus, for example, a complexity in the range of approximately 100 kb now permits hybridization to both sides of a tumor-

APPENDIX B

CLAIMS - US 6,414,133 (DIETZ-BAND)	PENDING CLAIMS	EXEMPLARY SUPPORT IN SPEC.
		specific translocation. The portion of the probe targeted to one side of the breakpoint can be labeled differently from that targeted to the other side of the breakpoint so that the two sides can be differentiated with different colors, for example." *p. 38, lines 8-16; ¶ 0141.* "32. High complexity nucleic acid probes for the detection of genetic rearrangements. 111. Nucleic acid probes, according to claim 32, comprising nucleic acid sequences that are substantially homologous to nucleic acid sequences in chromosomal regions that flank and/or extend partially or fully across breakpoints associated with cytogenetically similar but genetically different diseases." Original claims 32 and 111 See also, Fig. 11, and description below
said second probe set being sufficient in length and substantially complementary to nucleotides on both sides of the breakpoint region of a second DNA but less than an entire chromosome such that said second probe set will hybridize to both sides of the breakpoint region regardless of whether the second DNA has been broken in the breakpoint region and either end fused to another DNA.	said second probe set being sufficient in length and substantially complementary to nucleotides on both sides of the breakpoint region of a second DNA but less than an entire chromosome such that said second probe set will hybridize to both sides of the breakpoint region regardless of whether the second DNA has been broken in the breakpoint region and either end fused to another DNA.	see above; also "Figure 11 illustrates some exemplary probe strategies for detection of structural aberrations. . . . Section a) represents the use of a probe which stains a whole chromosome. . . . Section b) represents the reduction of the stained region of the chromosome shown in a) to that in the vicinity of a breakpoint. . . Section c) represents the use of a probe which binds to sequences which come together as a result of the rearrangement and allows for the detection in metaphase and interphase cells. In this case the different sequences are stained with different 'colors.' Such a staining pattern is

APPENDIX B

CLAIMS - US 6,414,133 (DIETZ-BAND)	PENDING CLAIMS	EXEMPLARY SUPPORT IN SPEC.
		that used in the examples of Section VIII of this application. . . . Section d) represents an extension of c) by including staining of both sides of both breakpoints involved in the rearrangement. Different 'colors' are used as indicated. The additional information supplied by the more complex staining pattern may assist with interpretation of the nuclei." *p. 31, line 1 - p. 32, line 19; ¶ 0122-0127.*
11. The probe set of claim 10, wherein said probes are detectably labeled.	136. The probe set of claim 135, wherein said probes are detectably labeled.	"Section III *infra* describes methods of rendering the probe visible. Since multiple compatible methods of probe visualization are available, the binding patterns of different components of the probe can be distinguished — for example, by color. Thus, this invention is capable of producing any desired staining pattern on the chromosomes visualized with one or more colors (a multi-color staining pattern) and/or other indicator methods." *p. 36, lines 17-23; ¶ 0137.*
12. The probe set of claim 11, wherein said first DNA is part of the ABL1 gene on chromosome 9 and the second DNA is part of the BCR gene on chromosome 22.	137. The probe set of claim 136, wherein said first DNA is part of the ABL1 gene on chromosome 9 and the second DNA is part of the BCR gene on chromosome 22.	"Specifically herein exemplified are chromosome specific reagents and methods to detect genetic rearrangements . . . that produce the BCR-ABL fusion which is diagnostic for chronic myelogenous leukemia (CML). Such chromosome specific reagents for the diagnosis of CML contain nucleic acid sequences which are substantially homologous to chromosomal sequences in the vicinity of the translocation breakpoint regions of chromosomal regions 9q34 and 22q11 associated with CML. Those reagents produce a staining pattern which is distinctively altered when the

APPENDIX B

CLAIMS - US 6,414,133 (DIETZ-BAND)	PENDING CLAIMS	EXEMPLARY SUPPORT IN SPEC.
		BCR-ABL fusion characteristic of CML occurs. Figure 11 graphically demonstrates a variety of staining patterns which, along with other potential staining patters, are altered in the presence of a genetic rearrangement, such as, the BCR-ABL fusion." *p. 19, line 22 - p. 20, line 8; ¶ 0075-0076.*
14. A diagnostic kit for detecting a structural abnormality caused by chromosomal breakage and rearrangement containing a reagent comprising at least one probe set of the probe set according to claim 10, and a container containing said reagent.	138. A diagnostic kit for detecting a structural abnormality caused by chromosomal breakage and rearrangement containing a reagent comprising at least one probe set of the probe set according to claim 135, and a container containing said reagent.	"This invention still further provides for test kits comprising appropriate nucleic acid probes for use in tumor cytogenetics, in the detection of disease related loci, in the analysis of structural abnormalities, for example translocations, among other genetic rearrangements, and for biological dosimetry." *p. 25, lines 8-12; ¶ 0095.*
15. A diagnostic kit according to claim 14 further comprising at least two containers, wherein a first container contains a reagent comprising said first probe set and a second container contains a reagent comprising said second probe set.	139. A diagnostic kit according to claim 138 further comprising at least two containers, wherein a first container contains a reagent comprising said first probe set and a second container contains a reagent comprising said second probe set.	*see claim 138, above*
16. A diagnostic kit according to claim 15 wherein said reagent comprises said first and said second probe sets.	140. A diagnostic kit according to claim 139 wherein said reagent comprises said first and said second probe sets.	*see claim 139, above*
17. A diagnostic kit for detecting a structural abnormality caused by chromosomal breakage and rearrangement containing a reagent comprising at least one probe set of the probe set according to claim 8, and a container containing said reagent.	141. A diagnostic kit for detecting a structural abnormality caused by chromosomal breakage and rearrangement containing a reagent comprising at least one probe set of the probe set according to claim 133, and a container containing said reagent.	"This invention still further provides for test kits comprising appropriate nucleic acid probes for use in tumor cytogenetics, in the detection of disease related loci, in the analysis of structural abnormalities, for example translocations, among other genetic rearrangements, and for biological dosimetry." *p. 25, lines 8-12; ¶ 0095.*
18. A diagnostic kit according to claim 17 further comprising at least two containers,	142. A diagnostic kit according to claim 141 further comprising at least two containers,	*see claim 141, above*

APPENDIX B

CLAIMS - US 6,414,133 (DIETZ-BAND)	PENDING CLAIMS	EXEMPLARY SUPPORT IN SPEC.
wherein a first container contains a reagent comprising said first probe set and a second container contains a reagent comprising said second probe set.	**wherein a first container contains a reagent comprising said first probe set and a second container contains a reagent comprising said second probe set.**	
19. A diagnostic kit according to claim 18 wherein said reagent comprises said first and said second probe sets.	**143. A diagnostic kit according to claim 142 wherein said reagent comprises said first and said second probe sets.**	*see claim 142, above*

Application Serial No. 10/608,092
028723-384

CERTIFICATE OF FACSIMILE TRANSMISSION

I hereby certify that this Communication is being facsimile transmitted to the U.S. Patent and Trademark Office on the date shown below.

Signature Sally Dankers Date: Sept 9, 2003

CLAIMS OF DIETZ-BAND ET AL. THAT DO NOT CORRESPOND TO COUNT

Claims 4 and 13 of the Dietz-Band et al. Patent claims are listed on the attached Form 850 as not corresponding to the count in agreement with the Request for Interference from the Gray et al. party. Said claims 4 and 13 of Dietz-Band et al. are directed to specific AML1 and ETO gene limitations for which Gray et al. do not have any supporting disclosure.

BENEFIT SUPPORT FOR CLAIMS OF GRAY ET AL. TO PRIORITY DOCS.

The instant specification of Gray et al. (Ser. No. 10/608,092) discloses continuations and divisional relationships back to Gray et al. (Ser. No. 07/537,305). Therefore, the support pointed to in the Request for Interference from the Gray et al. Party is also the support that provides benefit back to the filing date of said priority document: Gray et al. (Ser. No. 07/537,305; filed 6/12/90).